Review

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Continuous glucose monitoring: data management and evaluation by patients and health care professionals – current situation and developments

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Abstract: Continuous glucose monitoring (CGM) technology represents a valuable tool for diabetic patients to control and regulate their blood glucose (BG) levels and to reduce adverse metabolic states, for example, by defining glucose alarm thresholds that alert users if the glucose value crosses to an undesired range. Improvement of CGM technology is ongoing, but there are barriers which confine the usefulness of CGM systems. The utility is mainly defined by the operability of the specific device and also by the provided benefit of available CGM software solutions. In order to take best advantage of diabetes therapy, users should be adequately educated in how to use their CGM system and how to interpret the collected data. Different CGM software applications provide partially different CGM reports and statistics. The standardization of this information also would be conducive to the best possible diabetes management.

Keywords: continuous glucose monitoring system; continuous glucose monitoring; data evaluation; diabetes mellitus.

Introduction

Glucose monitoring is a key element in diabetes management. The monitoring of results allows determination of the degree of glucose metabolic disturbance. For people with intensified insulin therapy, it is essential to adapt therapeutic decisions like insulin dosing during daily life. Compared to traditional monitoring methods like self-monitoring of blood glucose (SMBG), continuous glucose monitoring (CGM) provides much more information, which can be used to better understand the causes and outcomes of shifting blood glucose (BG) levels throughout the day. However, the large amount of data provided by CGM systems can be quite challenging. Users therefore should be adequately educated on how to interpret and use safely the constantly updated glucose values and charts or trend arrows for therapy decisions [1].

CGM systems are one cornerstone of fully automated closed-loop insulin delivery systems, the so-called artificial pancreas systems (APS) [2]. Until a fully reliable artificial pancreas is developed, retrospective data analysis is one of the key elements to benefit most from CGM use. Retrospective data analysis helps in making therapeutically beneficial decisions but also preferably requires standardized data reports [3]. The ambulatory glucose profile (AGP), which is explained later in the text, is a good example of a standardized graphical report. It is intuitively interpretable, which makes it a useful tool for clinical practice [4].

Self-monitoring of blood glucose

Expedient control of BG in diabetes management demands precise and accurate measurements of BG concentrations traceable to a metrological standard. Before the noticeable rise in CGM use in recent years, diabetes control was typically accomplished by multiple daily capillary BG measurements, a procedure which requires fingersticks to get capillary blood for each measurement. Irrespective of that, the patient obtains only a snapshot of his or her BG
level. Moreover, information is provided neither about the expectable direction (rise or fall) of the BG level change within the next hours nor about the glucose levels before the measurement was performed. On this basis, it is difficult for diabetes patients to achieve their glucose level targets even with several BG tests a day [5].

Continuous glucose monitoring

In contrast to SMBG, where glucose is measured in capillary blood, CGM systems measure glucose levels in the interstitial fluid of the subcutaneous fatty tissue. Due to the different characteristics of capillary blood and interstitial fluid, both should be considered as discrete compartments [6]. Basu et al. [7] used glucose isotopes to determine the physiological lag time between BG measurements and measurements of interstitial fluid glucose in patients with type 1 diabetes. During steady-state conditions, they determined a time span of \(~7–10\) min until glucose transport from the intravascular to the subcutaneous interstitial fluid compartment could be observed [7].

CGM systems typically consist of three components: (1) a sensor that is inserted into the subcutaneous tissue and measures glucose levels continuously, (2) a transmitter which is attached to the sensor and (3) a receiver which displays glucose concentrations. In recent systems, the receiver device can also be represented by a smartphone (Figure 1) [8]. CGM systems usually display not only the current (latest) glucose value but also curves with individual values up to every \(~5\) min. Furthermore, trends (represented by arrows) which inform about rising or falling glucose levels can be visualized (Figure 2).

Currently, two different types of CGM systems are available on the market: Real-time continuous glucose monitoring systems (rtCGM) and intermittently scanned continuous glucose monitoring systems (iscCGM, flash glucose monitoring – FGM). rtCGM typically provides glucose values every 5 min (288 values/day) [5] with a sensor wear time of 6–10 days (rtCGM, non-implantable sensors) or up to 6 months (rtCGM, implantable sensors), and it has some essential advantages because (1) real-time data about the current glucose level is provided, (2) the efficacy of diabetes therapy decisions like insulin administration can be confirmed within a short length of time and (3) alarm signals which warn about impending or occurring hypoglycemic or hyperglycemic events can be individually defined and adjusted [9].

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

Figure 2: Display of a CGM system (scheme).
Only one novel rtCGM system provides factory calibration, all others have to be manually calibrated to BG two times per day.

The currently available iscCGM system provides glucose levels only after the sensor is actively scanned by the patient using a receiver or a compatible smartphone [5]. It is factory calibrated, has a sensor wear time of 14 days and 8 h of data are stored on the sensor and can be displayed after scanning with the reader. However, it provides no alarms between scans.

As CGM provides a comprehensive set of data, tracking glucose levels 24 h a day, it represents a valuable tool in preventing critical glucose metabolism conditions. With the help of visualized glucose levels, trends and statistics, patients can optimize their glycemic control to subsequently reduce the frequency and severity of, for example, hypoglycemic events [4].

A multitude of characteristics regarding CGM technology such as the duration of the operating life, accuracy, ease of use, data management and software solutions for data analysis have been improved since CGM was first introduced. At the same time, size, weight, complexity and cost of CGM systems have decreased [5]. However, the advantage of SMBG compared to CGM is that SMBG systems mostly are more accurate than CGM systems. This also is the reason why, until recently, CGM systems only were intended for adjunctive use, which means that CGM data should not be exclusively consulted as a basis for treatment decisions. For this, CGM data had to be verified by a fingerstick glucose measurement [10].

At present, three CGM systems [rtCGM: Dexcom G5, Dexcom G6 (Dexcom, Inc., San Diego, CA, USA); iscCGM: FreeStyle Libre (Abbott Diabetes Care, Alameda, CA, USA)] are being declared as providing partial replacement of BG measurements by their manufacturers. Therefore, glucose values may be used for therapy decisions. Except for measurements for calibration (in the case of manually calibrated CGM systems), additional measurements with a BG monitoring system are required in special situations defined in the respective device manuals [11].

Target groups

In June 2016, the German Federal Joint Committee (G-BA) decided that rtCGM-systems for adjusting treatment regimens of diabetic patients who are in need of an intensified insulin therapy would become a service of the statutory health insurance and thereby be included in contractual medical care [12].

The benefit of CGM is largest for patients meeting one or more of the following characteristics: hypoglycemia unawareness, nocturnal hypoglycemia, high glycemic variability, disliking the fingerstick method (widespread among children) and rapid changes in BG. Additionally, CGM offers the opportunity to remotely monitor the glucose metabolism of patients who are highly dependent on a caregiver’s nursing or to control a child’s glycemic status [13, 14].

User calibration vs. factory calibration

The measuring principle of the most common CGM systems is based on an enzymatic reaction which generates an electrical current that is proportional to the glucose concentration in the interstitial fluid. After calibration, the CGM system converts the signal of the electrical current into a displayed glucose concentration [15]. The calibration algorithms have markedly evolved over the years to better adapt the underlying mathematical model to conditions like glucose kinetics or non-physiological signal drift [16].

Calibration of CGM systems can be performed either by their users, during the manufacturing process or both. Most rtCGM systems require user calibration two times a day using a capillary BG measurement. The accuracy of the CGM is directly determined by the accuracy of the BG test results [17], which can be affected by user mistakes, the accuracy of the used meter and transcription mistakes of the glucose values including unacceptable delay lengths [18], or by choosing an inadequate point of time for calibration. Calibration of CGM systems should only be performed when glucose levels are stable [19].

The term “factory calibrated”, on the other hand, describes the calibration of a CGM system during the manufacturing process. Sensor sensitivity is determined by a sensor code which is preprogrammed into the sensors’ electronics. Factory-calibrated CGM systems avoid the need for manually performed calibrations and recalibrations, which is more convenient for the users and also excludes potential handling and transcription errors from the start [18]. However, if the factory calibration does not adequately reflect the user’s glucose values, there is no chance for correcting it and the sensor has to be replaced.

Therefore, a system that provides both factory calibration, and also optional manual calibration as it is
provided in the new Dexcom G6 system [20], could be potentially helpful.

Patient data use

As SMBG measurements provide only a snapshot of the current glucose level, various metabolic states of interest between two measurements are likely to remain invisible, especially if the measurements are timed disadvantageously. For example, postprandial rises in BG levels are usually not noticed in their actual extent and could tempt patients to make wrong therapy decisions once they are known (Figure 3). CGM data, on the other hand, enable displaying continuous timelines of glucose levels and thus clearly have potential to substantially supplement (and partly replace) BGM data and thereby to improve patients’ decisions. This advantage goes along with a much larger amount of data which needs to be collected. At this point, it is worth noting

Figure 3: In contrast to data provided by BGMS, CGM data reveal any glucose excursion, e.g. after meals or during physical activity. (A) BG information over one day provided by BGMS. (B) Comparison of the provided glucose information over one day by CGM (green) and BGMS (red). CHO, carbohydrates.
that CGM data always need to be assessed in context to the patients’ carbohydrate intake, insulin dosing and physical activity. Users should take this into account for their therapy during daily life and record corresponding events with as much detail as possible for retrospective interpretation.

Trend arrows can be very helpful, but should be used while also taking the curve, meal, insulin and activity of the last hours into account. In times of direction change of the glucose dynamics, the trends might react slowly which patients have to consider before they perform therapy adaptations [21].

Due to the amount of data and the differences between SMBG and CGM, uninformed patients might be tempted to overreact in some situations. As a consequence, despite all of the benefits CGM technology is able to provide compared to SMBG, adequate user education is essential for achieving good clinical outcome.

By now, one training program developed by the manufacturer of the currently available iscCGM system [22] and one manufacturer-independent training program for rtCGM systems (SPECTRUM), which was developed by two working groups (AGDT and AGPD), are available in Germany [23].

In recent years, a growing group of diabetic patients developing so-called do-it-yourself artificial pancreas systems (DIY APS) has emerged. These patients use homemade algorithms and controllers to fully automate their insulin supply based on CGM data [24]. Although DIY APS users report improved therapeutic outcomes [25, 26], these results cannot easily be compared to those of more rigorous scientific approaches, like randomized controlled trials. Furthermore, differentiating between improved outcomes caused by DIY APS as opposed to the (often coinciding) patients’ increased engagement in their therapy may be hard [27]. Another issue with DIY APS may be that manufacturers of the devices used are potentially no longer liable in case of device failures if the device is driven by a DIY APS and, thus, being used off-label [28, 29]. For tech-savvy persons, DIY APS algorithms may pose less risk than for non-technical persons. Furthermore, worldwide no fully closed-loop system and only one hybrid closed-loop system are currently approved in the United States (Medtronic 670G; Medtronic, Northridge, CA, USA) which complicates the legal situation of DIY APS [24].

**Retrospective data interpretation**

The virtually endless amount of data generated by CGM systems and evaluable by the associated software is unquestionably a great benefit of CGM technology, but this fact might also discourage those who have to work with these data. Finding helpful therapy advice and decisions is not easy as data reports can be quite confusing, which is why there remains a request from patients, clinicians, providers and researchers to see improvements in making the technology not just more accurate but also more convenient [30]. One key challenge in establishing an adequate understanding of glycemic variability therefore is to evolve standardized methods of glucose data analysis and standardized reports about the outcomes of those. A desirable report is a short and well-structured summary which reveals the important patterns of glucose variability. Aside from that, standardized definitions and metrics not only would facilitate assessing patient status but also would allow clinicians to make more accurate and substantiated therapy adjustments because therapy progress can be compared from visit to visit.

Retrospective analysis and interpretation of CGM data is the key to benefitting from CGM use as therapeutic decisions can be underpinned [31, 32]. For retrospective data analysis, data must be downloaded either to local storage [33] or data are stored cloud-based. Most CGM manufacturers use cloud-based storage nowadays [34]. Subsequent data analysis is then made possible by several software solutions, both manufacturer-specific and third party, allowing clinicians to evaluate the measured glucose patterns [31, 32].

**Statistical information**

A variety of statistical information and graphic visualization possibilities exist but CGM data should be qualified before they are assessed. This means the reliability and representativeness of the obtained data with respect to the users’ true patterns have to be confirmed. Therefore, it is important to (1) ensure that the clock and date are set correctly on the receiver device and on the CGM software containing device, that (2) all required calibrations were carried out correctly, that (3) the conditions during which data collection happened are clarified (e.g. stress, illness, medication, travel and others have an extenuating effect on glucose measurements), that (4) the data are, to a certain extent, accurate [35] and that patients are compliant and wear the CGM system reliably.

Device manufacturers often provide proprietary and brand-specific software solutions or collaborate with independent software providers, but also non-brand specific software solutions are available [33]. Statistics provided by CGM software usually include the information given in Table 1.
The variability parameter standard deviation, and the parameters estimated hemoglobin A1c (HbA1c) and time in range, which have the potential to monitor diabetes control, are further explained below.

*Standard deviation*: A high standard deviation results from many glucose values being located markedly above and below the average, which can be caused, for example, by glycemic variability [36] or insufficient calibration algorithms [37].

*Estimated HbA1c*: HbA1c is recommended as the key laboratory parameter for monitoring diabetes [38], and it reveals the amount of glycated hemoglobin in blood (HbA1c) and thus provides information about a patient’s average BG levels during the previous 8–12 weeks [39]. Based on calculation rules, HbA1c is sometimes estimated based on average glucose concentrations [40].

*Time in range*: This parameter describes the percentage of time spent outside (above or below) and inside a desired target glucose range. Target ranges can be defined in each software program and it is advisable to adjust the limits individually for each patient. As a result, clinicians as well as patients can orient themselves by a simple glucose profile and are able to develop an individualized action plan aimed at adjusting therapy to reduce the amount of high or low glucose patterns. The analysis of time in range also helps evaluate effects of changes regarding a diabetic patient’s therapy [35]. Time in range might be considered to be a more useful parameter than HbA1c as glucose fluctuations are captured continuously and the parameter is more sensitive than HbA1c [41]. Furthermore, effects of patient-specific variations are less likely to considerably impact the value’s significance [42].

Further research is needed to assess the future value of the above mentioned parameters for diabetes control.

### Data visualization

It has become obvious that the use of CGM technology provides no substantial benefit in therapy if users do not know how to interpret the specific statistics and variables. Patients and clinicians must be able to easily conceive the data of interest. This requires easy attainability of the desired reports. Data must be portrayed organized, well-structured and in such a way that patterns can be identified promptly [15]. In an international consensus on use of CGM in 2017, physicians, researchers and qualified diabetic patients elaborated recommendations to advance standardized reporting and data analysis. Their key findings include standardized tools like AGP; reporting CGM data in due consideration of clinical conditions like hypoglycemic events or ketoacidosis; use of standardized metrics to facilitate the clinical workflow and a minimum of 14 consecutive days of data generation with a minimum of 70% of possible CGM readings [43].

Examples for data visualization can be found, for example, on the web pages of CGM system manufacturers.

### Ambulatory glucose profile

Together with the International Diabetes Center (IDC) (Minneapolis, MN, USA), Mazze et al. [44] developed an approach targeting the aim of electronically generated standardized reports for patients, clinicians and other health care providers to visualize glucose patterns and trends and make them easy to interpret. This approach is called the “AGP”. AGP reports for CGM data are generated by combining all data from several days or weeks and translating them into one period with the length of 24 h.

An AGP report contains different calculations and visualizations whose interpretation is facilitated by accompanying descriptive literature. Key elements are the following: (1) a plotted median curve (50th percentile), which depicts glucose stability. (2) Two curves right above and below the median which represent the interquartile range (IQR). The IQR shows the glucose range in which 50% of all data points are located and therefore describes glucose variability. (3) On the sides of the IQR are the 10th and 90th percentile curves, which allow tracing back extreme glucose excursions. On the basis of these data, it is possible to easily recognize specific patterns which
influence glucose variability and/or stability [45]. An expert group of 16 diabetes specialists from five European countries came to the conclusion that an AGP report usefully serves as an entry point for data analysis of CGM data [4].

The AGP tool is helpful for health care professionals and patients as the first step in assessing CGM data and educating patients. To evaluate further aspects and not to miss a single hypoglycemic event, it is important to use other graphical displays (e.g. single curve) of the software. The insulin dosage, food intake and activity must be considered together. Daily data [4] or other parameters of particular interest, therefore, also should be reviewed and assessed.

Data sharing and privacy

Some CGM systems allow sharing of rtCGM data (e.g. via smartphone) with other eligible persons, which enables a remote monitoring of, for example, a child’s glucose pattern at any time (e.g. during the night or when the child is not at home) [13, 14]. Although remote monitoring technology was already available more than 20 years ago, widespread use of devices with sufficient computational power, like smartphones, and increasing coverage by communication lines (i.e. internet access through landlines or mobile networks) provided improved tools for remote monitoring [46]. These technologies also play a crucial role in the development of APS and DIY APS.

However, even CGM systems which do not specifically offer that option generate data that needs to be aggregated and stored for further processing and interpretation. This is often implemented using cloud-based services [47]. Independent from cloud-based services, manufacturers often have the opportunity to obtain patients’ usage data and to use it as declared in their privacy policy as long as the respective software connects to the Internet. In addition, the opportunity to share data with third parties like clinicians is frequently provided.

Remote glucose monitoring, especially by health care professionals, may help improve therapy and patient-reported outcomes in different population groups [48–50].

Although cloud-based data storage facilitates data management and assessment, it is a meaningful privacy and security risk not only with regard to cyberattacks. Data directly associated with the patient’s disease and also data like internet protocol (IP) addresses or other browsing activities whilst using the respective applications and platforms may be affected [47]. Diabetic patients therefore are well advised to find out how their personal data and information are used.

Another source of risk could be the physical CGM system itself. A major issue in medical devices is the accessibility of the device by unauthorized persons. As CGM systems rely on the wireless transfer of data, the level of encryption of transmitted data is crucial [47].

Future developments

Modern CGM sensors usually allow direct data transfer to smartphones, which replace traditional CGM receivers. Combined with data provided by other medical devices such as SMBG monitors, insulin pumps, insulin pens and also other wearable sensors not specifically developed for diabetes control, this allows the generation of large data pools [51, 52]. Other sensors are portrayed by, for example, smart clothes, smart watches or sensors for biomarkers based on tears, saliva, sweat or breath [53]. With regard to diabetes, an “ecosystem” of data around the disease thereby is provided and could allow the identification of environmental factors that influence the onset and course of diabetes. Additional data from clinical registries, electronic health records, prescription entries and quality of life and health surveys allow psychosocial and economic contextualization of CGM data [54].

Based on those data pools, software solutions could calculate prediction models which support taking proactive medical decisions. By the implementation of pattern recognition and risk models, dashboards to identify diabetic patients with high risks of developing diabetes-related complications could be designed. However, the development of proactive medicine applications is dependent on the reliability of data sources [55, 56].

Conclusions

Although BG meters are more accurate, a big advantage of CGM compared to SMBG is that glucose levels can be monitored continuously, and thus CGM data provide a much more detailed picture of the patients’ glucose metabolic state. Thereby, on the one hand, patients using CGM have the ability to react quickly to their glucose levels and subsequently to avoid hypo- and hyperglycemia more reliably. Clinicians and patients can take therapy decisions on a more profound basis than enabled by SMBG. Data sharing and cloud-based storage provide interesting new possibilities, but add a possible data security risk.
However, it is important to check data validity and to interpret the large amount of data correctly. User education in the use of CGM data is obligatory.

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