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Continuous Glucose Monitoring: the achievement of 100 years of innovation in diabetes technology

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Summary:

Monitoring of glucose levels is essential to effective diabetes management. Over the past 100 years, there have been numerous innovations in glucose monitoring methods. The most recent advances have centered on continuous glucose monitoring (CGM) technologies. Numerous studies have demonstrated use of continuous glucose monitoring confers significant glycemic benefits on individuals with type 1 diabetes (T1DM) and type 2 diabetes (T2DM). Ongoing improvements in accuracy and convenience of CGM devices have prompted increasing adoption of this technology. The development of standardized metrics for assessing CGM data has greatly improved and streamlined analysis and interpretation, enabling clinicians and patients to make more informed therapy modifications. However, many clinicians many be unfamiliar with current CGM and how use of these devices may help individuals with T1DM and T2DM achieve their glycemic targets. The purpose of this review is to present an overview of current CGM systems and provide guidance to clinicians for initiating and utilizing CGM in their practice settings.

Keywords

Continuous glucose monitoring; CGM; real-time CGM; rtCGM; intermittently scanned CGM; isCGM; type 1 diabetes; type 2 diabetes; HbA1c; Ambulatory Glucose Profile; AGP

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Declaration of Competing Interest

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1. Introduction

Innovations in glucose monitoring have resulted in the development of continuous glucose monitoring (CGM) systems, which have been shown to confer significant benefits in improving glycemic control. [1–11] Although adoption of CGM is steadily increasing, use of this technology has been centered mainly in endocrinology and diabetes specialty practices. As such, many primary care physicians may be less familiar with CGM and how it can benefit their patients with diabetes. The purpose of this review is to present an overview of current CGM systems and provide guidance to clinicians for initiating and utilizing CGM in their practice settings.

2. Evolution of Glucose Monitoring

The field of glucose monitoring has progressed significantly over the last 100 years, since Stanley Rossiter Benedict published his seminal work on analytical methods for measuring urinary glucose.[12] The Benedict's Solution/Assay was the main test for diabetes monitoring for the next 50 years, until the glucose-oxidase based reactions were discovered in the late 1950's, [13] and later adapted to be used in clinical laboratories to measure plasma glucose – initially manually, and currently by automated methods [14]

Since then, there were several advances in the development of glucose test strips, but it was not until the late 1970s to early 1980s that the concept of self-monitoring of blood glucose (SMBG) with glucose meters became more widely applied. [13] The next stage was the development of continuous glucose monitoring (CGM) around this time, but the first CGM was not commercially available until 1999.[15] However, these initial CGMs had limited use in clinical settings.

Several revolutionary advances in CGM technology have occurred with improved accuracy, use of smaller and less invasive devices, extended sensor life, approval for insulin dose decisions and with the elimination of finger-sticks need for capillary glucose measurements in factory-calibrated CGMs, thereby decreasing the patient's burden of diabetes care. All these advances have led to better patient's satisfaction and adherence with device use and medication therapy, increased awareness by clinicians and a significant increase in CGM use, mostly in patients with T1DM, but also in patients with T2DM treated with intensive insulin regimens.[16–19]

Improvements in CGM technology has also permitted remarkable advances in the integration with continuous subcutaneous insulin infusion (CSII) or insulin pumps, and further development of automated insulin delivery systems, or "closed-loop systems", along with the creation and validation of newer CGM-based glycemic metrics, beyond SMBG and HbA1c.[20]

3. CGM

3.1 Rationale for CGM

Although SMBG remains an important tool that guides glycemic management strategies and decision-making for patients with DM and their clinicians, it can provide point-in-time

measurements of current glucose levels, with no predictive information about impending glucose levels. Whereas, CGM devices present both the current glucose level and rate of change (ROC) trend arrows, indicating the direction and rapidity of changing glucose. These data enable patients to respond immediately to mitigate or prevent acute glycemic events and allow patients to make better informed decisions in their medication requirements and other areas of their daily diabetes self-management. Moreover, historical data can be viewed in the device reader/receiver or smartphone app and downloaded for retrospective analysis by patients with diabetes and their clinicians.

3.2 Personal CGM Technologies

There are currently two types of personal CGM system technologies available: real-time CGM (rtCGM) and intermittently scanned CGM (isCGM), which is often referred to as “flash” CGM. Current rtCGM systems include the Dexcom G6 (Dexcom, Inc., San Diego, USA), Medtronic Guardian Sensor 3 (Medtronic, Inc., Northridge, USA) and Senseonics Eversense (Senseonics, Inc., Germantown, USA). Relevant features of the current personal CGM devices are presented in Table 1.

The Guardian Sensor 3 and Dexcom G6 systems comprise three components: a disposable wired sensor inserted in the subcutaneous tissue; a transmitter that is attached to the sensor; and a receiver (handheld or smartphone) that displays the glucose data. The Dexcom G6 can be used with the receiver and smartphone app, whereas, the Guardian Connect is used only with a smartphone app. The Eversense rtCGM consists of a sensor implanted by a clinician into the subcutaneous tissue in the upper arm; an external transmitter that is secured above the sensor; and a smartphone app, which serves as the receiver. The most current isCGM system is the FreeStyle Libre 2 (Abbott Diabetes Care, Alameda, USA). The system comprises two components: a sensor/transmitter unit that is inserted in the upper arm; and a handheld touchscreen reader device or a smartphone app (LibreLink). Both the rtCGM and isCGM technologies are available as standalone devices. Furthermore, Guardian 3 and Dexcom G6 can be linked to sensor-augmented insulin infusion pumps or automatic insulin delivery (AID) systems.

A key differentiator between the two CGM technologies is how data are delivered to the user. RtCGM systems automatically transmit data to the patient’s receiver and/or smartphone. In contrast, isCGM systems require the patient to “swipe” the receiver close to the sensor to obtain current and historical glucose data. However, if more than 8 hours occur between scans, only the most recent 8 hours of data will be retained and available for review.

An important feature of both rtCGM and isCGM systems is the ability to alert users when glucose levels are rising above or falling below the target glucose range. Both technologies allow users to set high and low alarms/alerts. In addition, the Dexcom G6 system has a predictive “urgent low soon” (ULS) glucose alarm at 55 mg/dL [3.1 mmol/L].[21] This advanced warning has the ability to alert users when glucose is predicted to drop below 55 mg/dL [3.1 mmol/L] and been shown to be effective in reducing hypoglycemia among rtCGM-experienced users.[22] The Guardian Connect CGM System (Medtronic, Northridge, CA, USA), including the Enlite™ glucose sensor and the Guardian Connect

Transmitter has similar predictive low glucose alerts plus a predictive high alert feature as well.[23]

An added safeguard of some current CGM systems is the ability to share data with clinicians, caregivers and family/friends in which glucose data and alarms/alerts are shared with family/friends and caregivers. A recent retrospective analysis of device usage and glycemic control in 15,000 children and adult found that real-time sharing CGM data was associated with improved device utilization and glycemic control.[24]

3.3 Professional CGM Technologies

Professional CGM consists of a real-time or masked CGM that is worn by patients for short periods (typically 6–14 days). The clinician uses the CGM data to assess patient glycemic status, make changes to treatment regimens to achieve glycemic targets and provide patient education. Three professional CGM systems are currently available: Dexcom G6 Pro CGM system; Medtronic iPro2 Professional CGM system; and FreeStyle Libre Pro system. The Dexcom G6 Pro CGM system can be programmed to provide real-time masked or unmasked data over 10 days. [25] Accordingly, it can also be used by patients as a trial for personal CGM or to get near immediate feedback about the impact of lifestyle or therapy decisions on glycemia. The iPro2 system provides masked retrospective data for up to 6 days. [26] The FreeStyle Libre Pro system provides masked retrospective data up to 14 days. [27]

4.0 Evidence of Efficacy and Safety

4.1 rtCGM

The clinical efficacy, safety and other benefits of rtCGM use in individuals with T1DM and T2D, regardless of the insulin delivery method used, have been demonstrated in numerous studies. [1, 2, 41–50] The large, randomized DIAMOND trials showed improved HbA1c, reduced time spent in the hypoglycemic and hyperglycemic ranges and reductions in moderate to severe hypoglycemia in individuals with multiple daily injections (MDI)-treated T1DM and T2DM using rtCGM compared with traditional SMBG.[1, 2] Investigators also reported significant reductions in diabetes-related distress and greater hypoglycemic confidence among the rtCGM users, [45] Importantly, findings from a recent randomized trial found that rtCGM use significantly increased time spent in normoglycemia and reduced severe hypoglycemia in among individuals with impaired hypoglycemia awareness.[48]

Similar results were shown in the recent HypoDE study, which investigated rtCGM use vs. SMBG in MDI-treated T1DM adults with problematic hypoglycemia (e.g., impaired hypoglycemia awareness, frequent severe and/or nocturnal hypoglycemia).[8] Compared with SMBG, rtCGM use was associated with fewer low glucose events and episodes of severe hypoglycemia.

Studies have also that rtCGM as a component of sensor-augmented insulin pumps (SAP) with predictive low glucose suspend (PLGS) functionality reduces the incidence and severity of hypoglycemia,[51–53] suggesting that automated suspension of insulin infusion in response to impending low glucose can assist individuals with T1DM avoid hypoglycemia without significantly increasing hyperglycemia.[51] Use of a hybrid closed-loop (HCL)

insulin delivery system also showed notable reductions in HbA1c, glycemic variability and time spent in the low glycemic ranges, as well as improved time in target range.[52]

Advances in automated insulin delivery research have led to the development of hybrid and advanced hybrid closed-loop control (CLC) systems, which utilize integrated CGM-insulin pump systems with algorithm-driven controllers that automatically control delivery of basal insulin and correction boluses. Randomized controlled trials and meta-analyses have consistently shown that use of CLC insulin delivery systems can improve glycemic control, increase time in range and reduce hypoglycemia risk in pediatric and adult T1DM patients.[54–58] Most recently Brown et al. investigated use of a CLC system in 168 adolescent and adult patients with T1DM who were randomized 2:1 to CLC or sensor-augmented insulin pump therapy and followed for 6 months.[59] Investigators reported that use of the CLC system was associated with a higher percentage of time in target glycemic range compared with sensor-augmented pump (SAP) in experienced users. In a follow-up trial, 109 CLC-users from the previous study were randomly assigned to CLC or treatment with a hybrid closed-loop (HCL) system with low glucose suspend (LGS) and followed for an additional 3 months.[60] Switching to the HCL system resulted in reduced time in range and with increased HbA1c; however, similar reductions in hypoglycemia were observed in both groups. A recent study by Breton et al. showed that use of a CLC system resulted in a higher percentage of time in glucose range in T1D children compared with a sensor-augmented insulin pump.[61] The next step in CLC research is the development of systems that provide full closed-loop control that alleviates the need for meal announcements, alerts/alarms and ongoing maintenance.

4.2 isCGM

Use of isCGM has been associated with reductions in hypoglycemia, increased time in range, lower glycemic variability and improved patient satisfaction in individuals have been associated with isCGM use in randomized controlled trials with well-controlled T1DM [4] and T2DM [6] who were treated with intensive insulin therapy. In the IMPACT study, use of an earlier generation FreeStyle Libre system was associated with a 38% reduction in time spent in hypoglycaemia (<70 mg/dL), with increased time in range and reductions in glycemic variability.[4] Similar results were reported in the REPLACE study, which showed an association between FreeStyle Libre use and a 43% reduction in time spent in hypoglycemia in a large T2DM population treated with intensive insulin therapy.[6] Although reductions in HbA1c were not seen in either of these two randomized controlled trials, recent prospective, observational studies have demonstrated significant reductions in HbA1c [9–11, 62, 63] and hypoglycemia [9–11, 62] compared with SMBG within large T1DM and T2DM populations. Moreover, some of these studies also showed significant reductions in hospitalizations for hypoglycemia [9, 10] and absenteeism.[9, 10]

5. Beyond HbA1c: Rationale for Clinical Use of CGM Metrics

HbA1c has been long considered the gold standard in assessing the risk for long-term microvascular and macrovascular complications. However, the accuracy of HbA1c test results can be falsely high or low in numerous conditions such as iron deficiencies,[64]

anemia,[65] hemoglobinopathies[66] and chronic kidney disease. [67] Pregnancy[68] and ethnic and racial differences in glycation rates[69–71] are also linked to inaccuracies in test results. It has also been shown that a single HbA1c value may encompass a wide glucose range.[72] For example, whereas the mean glucose range for an HbA1c value of 8.0% (64 mmol/mol) is 155 to 218 mg/dL, the mean glucose for an HbA1c value of 7.0% (53 mmol/mol) ranges from 128 to 190 mg/dL.[72] Moreover, HbA1c testing provides no information about the frequency and magnitude of acute intra-day glycemic excursions or overall glycemic variability. Despite these limitations, HbA1c testing is a valuable tool when used in conjunction with CGM data. Moreover, HbA1c remains an accepted quality metric for assessing effectiveness and quality of care by HEDIS (HealthCare Effectiveness Data and Information Set), with potential impact on reimbursement.

5.1 New CGM-Based Glycemic Metrics

In 2017, an expert panel met to develop consensus recommendations for interpreting CGM data and identified 14 key CGM metrics for assessing glycemic status.[73] In 2019, the panel reconvened to develop specific CGM targets relevant to these metrics in order to assist clinicians and patients with diabetes in interpreting and utilizing CGM data in routine clinical care.[74] (Table 2)

Among the 10 core metrics selected for use in clinical care, the panel identified three metrics that could be used as an initial starting point for assessing glycemic status: time in range (TIR: 70–180 mg/dL [3.9–10 mmol/L]), time below range (TBR: <70 mg/dL [<3.9 mmol/L]; <54 mg/dL [<3 mmol/L]); and time above range (TAR: >180 mg/dL [>10 mmol/L]; >250 mg/dL [>13.9 mmol/L]).[74] As reported by Beck et al. [79] and Vigersky et al., [80] TIR has been shown to closely correlate with HbA1c values. (Table 3) TIR has also been to closely correlate with peripheral neuropathy in T2DM and chronic renal disease, [81] and it has been recommended as an outcome measure for future clinical trials. [82]

To further simplify data interpretation, the panel recommended use of a composite metric, TIR/TBR, focusing primarily on reducing TBR while increasing TIR. This approach would reinforce the need to reduce time in hypoglycemia, and at the same time, reduce time spent in hyperglycemia. As shown in Table 4, the specific targets time spent in these ranges were adjusted according to hypoglycemia risk. For example, the tighter target for time spent <70 mg/dL (<3.9 mmol/L) among older and/or high-risk patients was offset by a more relaxed target for time spent >250 mg/dL (>13.9 mmol/L).

5.2 Standardized CGM Data Presentation

In their consensus guidelines for use of CGM metrics, the expert panel recommended adoption of the ambulatory glucose profile (AGP) as a standardized template for displaying CGM metrics. [83, 84] (Figure 1) The AGP report facilitates rapid assessment of TIR, TBR and TAR, as well as other metrics, such as average glucose and the glucose management indicator (GMI) calculation. [77] Glucose variability is presented as a percentage coefficient of variation (%CV), with the recommended goal of <36%. [78] The composite glucose profile and daily profiles allow clinicians and patients to quickly identify problematic glucose patterns, which facilitate more informed clinical decision making and enhance

patient-clinician collaboration. Many CGM manufacturers and third-party developers have adopted the AGP as a template for their own download software.

5.3 CGM Data Interpretation

An important feature of current CGM systems is the ability to transmit glucose data to clinicians for retrospective analysis to identify problematic glycemic patterns that require attention. Clinicians can then provide feedback via in-clinic visits or telehealth technologies (e.g., phone, text, video conference) to counsel patients as needed. Although several approaches for interpreting data have been proposed,[85–89] clinicians who are less familiar with CGM may want to consider a 5-step process for interpreting AGP reports. (Table 5)

6. Implementing CGM in Clinical Practice

6.1 Workflow and Staff Training

The first step in CGM implementation is establishing a defined workflow that identifies the individual(s) who will be responsible for downloading/obtaining CGM data, displaying the data for analysis, entering data in patient records (scanned or electronically) and printing out reports for each patient. Areas of proficiency should include:

- Device setup, troubleshooting and awareness of common questions, problems and concerns.
- Ability to download and interpret device data (e.g., glucose, insulin administration), change device settings as needed, and adjust therapy.

All CGM manufacturers offer comprehensive, on-line training/education materials for their device. Guidance documents for interpreting/utilizing data, specifically, use of ROC trend arrows, are also available. These resources are presented in Supplementary Table 1.

6.2 Patient Selection

Although use of CGM was initially focused patients treated with intensive insulin therapy, a growing body of evidence is now demonstrating its value in patients on less-intensive treatment regimens.[90–93] Because the various CGM systems offer different features and functionalities, it is important to collaborate with patients to help them select the system that best meets their clinical needs, lifestyle, motivational level, cognitive capabilities and socioeconomic status. The following is a list of patient characteristics that may benefit from CGM use:

- Treated with intensive insulin regimens (MDI or insulin pump).[1–3]
- Increased risk for hypoglycaemia, impaired hypoglycaemia awareness, frequent nocturnal hypoglycaemia, frequent severe hypoglycaemia.[8, 48, 94]
- Pregnant with pre-existing T1DM,[95, 96] T2DM [95] or gestational diabetes. [97]
- Newly diagnosed T2DM (for episodic use as an educational tool). [93]

- T2DM patients not on intensive insulin regimens who are under good control but may benefit from full-time or episodic CGM as an alternative to SMBG. [93]

6.3 Patient Education and Training

Training is essential to optimizing use of CGM,[98–100] and it should begin with "refresher" instruction on strategies for prevention and treatment of hypoglycemia and hyperglycemia. For patients treated with intensive insulin regimens, clinicians should also confirm each patient's skills in calculating insulin doses, utilizing current glucose levels and individualized insulin parameters (e.g., insulin-to carbohydrate ratio(s) [I:CHO], insulin sensitivity factor(s) [ISF]) and anticipated carbohydrate intake.

When providing training on the selected device, clinicians should make sure that patients understand that the CGM measures glucose in the interstitial space and the values may be different than a blood glucose number. Typically, these are within 20% above 100 mg/dL (5.6 mmol/L) or < 20/mg/dl when glucose is less than 100 mg/dl (5.6 mmol/L). Training for using the CGM does not need to be complex. A simple 1-page instruction sheet was developed to support Engagement with CGM systems and to help optimize glycemic outcomes.[101] The initial topics to cover during the training session include:

- Procedures for setting the target range(s) and alarms/alerts.
- Sensor placement and insertion technique.
- Situations that will require confirmatory fingerstick test.
- Significance and functionality of the trend arrows.
- Procedure for downloading CGM data for personal use and for transmission to the clinician.
- How to use set up and use the data share function (if available)
- How to check for skin problems, sensitivity and allergic reactions that may be caused by the sensor adhesion material.

Clinicians should schedule close follow-up training to focus on use of trend arrows for insulin dosage and adjustment and activity/nutrition modification, interpretation and use of retrospective CGM data and use of data sharing functions. It is important that clinicians manage patient expectations in terms of what CGM can and cannot do and the time and effort required to integrate use of CGM into their daily lives.

7. Looking to the Future

7.1 Pregnancy

Another area where the value of CGM has been demonstrated is pregnancy. In a recent 12-month, randomized controlled study of 325 T1DM women who were pregnant or planning pregnancy, use of CGM vs. SMBG was associated with significantly increased TIR compared (p=0.0034) and shorter hospital stays (p=0.0091), with few neonatal intensive care admissions with >24-hour duration (p=0.0157), less neonatal hypoglycemia (p=0.0250) and lower incidence of large for gestational age (p=0.0210). [96] Although CGM use in

pregnancy was historically been considered to be off-label, the Dexcom G6, FreeStyle Libre 2 and Guardian Connect are approved for use in pregnancy in some European countries, but not in the U.S.

7.2 CGM Use in Renal Disease

It is well recognized that glucose and insulin metabolism in patients with diabetes are negatively impacted by end-stage renal disease (ESRD).[67] Although HbA1c testing in conjunction with SMBG is the recommended approach to assess glycemic control in diabetes patients with ESRD,[102] the accuracy and utility of these testing methods is severely limited due to susceptibility to numerous ESRD-related factors that can impact accuracy of results.[67] Use of CGM has the potential to overcome these limitation and facilitate identification of problematic glucose patterns and improve therapy management in these patients;[67, 103] however, CGM devices are not currently approved for use in dialysis patients.

In a 12-week pilot study by Joubert [104] et al., 15 dialysis patients with diabetes were monitored with SMBG three times daily for six weeks and then transitioned to CGM for an additional six weeks. Glucose profiles from both testing methods were used to guide therapy. [104] Mean CGM glucose dropped from 8.3±2.5 mmol/l to 8.2±1.6 mmol/l after SMBG but then significantly to 7.7±1.6 mmol/l ($P<0.05$) at the end of the CGM period without increased risk of hypoglycemia. Investigators also reported more frequent treatment changes using CGM vs. SMBG data.

7.3 Use of CGM during Radiologic Procedures

Concerns about component damage and patient safety have prompted most CGM manufacturers to warn users against wearing their devices when undergoing radiologic procedures, including magnetic resonance imaging (MRI), computed tomography (CT), and diathermy. [21, 32, 39] However, as stated in their safety labeling, their devices have never been tested under those conditions. The only exception is the Eversense CGM system, for which “non-clinical” testing has shown that the implanted sensor is not affected by MRI, as long as the strength of the static magnetic field remains within certain limits. [40]

The effects of radiologic procedures on CGM technologies have not been well studied. However, a recent in vitro study by Thomas et al. casts considerable doubt on the necessity for removing CGM devices when undergoing these procedures. [38] Investigators assessed the accuracy and functional integrity of wearable components of the Dexcom G6 system when exposed to therapeutic x-ray at a cumulative dose of 80 Gy and MRI, using radiofrequency fields (RF) oscillating at 64 or 128 MHz and magnetic fields of 1.5 or 3 T. Following these exposures, the reported glucose concentrations were similar to those displayed in the unexposed devices. The displacement force of 306g during the MRI exposure did not dislodge the sensor from the substrate. Moreover, the glucose data stored in the transmitter before exposure to MRI and x-ray remained intact. In addition, in a recent study of the Dexcom G6 sensor during elective abdominal surgery, investigators reported that glucose values were consistent and acceptable, suggesting that use of the device may be appropriate for peri-operative glucose management. [105] An in-vitro and small (n=10

sensors) study of the FreeStyle Libre Pro sensor showed no interferences from CT, MRI, x-ray or radiotherapy (RT).[36]

7.4 CGM Use in Hospital Settings

The COVID-19 pandemic has placed significant pressure on hospital staff to provide care to a growing number of individuals who present with severe SARS-CoV-2 infection. Diabetes and stress-induced hyperglycemia is a common scenario and is associated with poor outcomes in patients with COVID-19, [106–108]

Although early studies of CGM in hospitalized patients have been limited mostly to intravenous CGM technologies, [109–113] use of minimally-invasive and factory-calibrated CGM technologies have not been well studied. Nevertheless, in April 2020. the U.S. Food and Drug Administration (FDA) issued a new policy to expand the availability and capability of non-invasive remote monitoring devices [e.g., CGM] to facilitate patient monitoring while reducing patient and healthcare provider contact and exposure to COVID-19 for the duration of the COVID-19 public health emergency. [114] Albeit, this does not represent FDA approval for use of CGM in the hospital. In a recent study by Galindo et al, use of isCGM in hospitalized T2DM patients was associated with higher detection rate of hypoglycemic events (nocturnal and prolonged events) compared with standard point-of-care blood glucose testing. [115] In addition to this s, the advantages of using rtCGM devices with remote monitoring features (e.g., Dexcom G6 Follow and Abbott FreeStyle LibreLinkUp apps) reduces both staff exposure to infection and utilization of personal protective equipment.[116] A few studies using the Dexcom G6 system have shown reductions in hypoglycemia [117] and hyperglycemia among non-critically ill hospitalized patients. [118] Although CGM has the potential to become widely accepted for monitoring glycemic status in hospitalized patients, additional studies are needed to support continued use.

8. Summary

Over the last 100 years, advances in glucose monitoring have led to an array of innovative tools that have enabled patients with DM to improve their glycemic status and the quality of their lives. With ongoing improvements in CGM and insulin delivery technologies, patients and their healthcare providers now have the ability to fine tune therapy and, at the same time, reduce the burden of diabetes.

The recent adoption of standardized CGM metrics and integration of the AGP template into data download software has greatly simplified data interpretation, thereby increasing the feasibility of CGM use in primary care settings. As emerging evidence continues to demonstrate the benefits of CGM among patients with diabetes treated with less-intensive or non-insulin therapies, CGM may soon become a standard of care within the broader diabetes population. Moreover, primary care clinicians or their staffs will need to acquire requisite knowledge and skills to be able to effectively manage patients using CGM technologies.

In response to the COVID-19 pandemic, there is a rapidly growing interest in use of telemedicine technologies, which will further expand use of CGM and sensor-driven insulin

delivery devices. The pandemic has also triggered, at least temporarily, the need for using CGM in hospital settings where its value in improving glycemic control is compounded by providing additional safeguards for hospital staff and reducing utilization of personal protective equipment. However, expanding use of CGM and other diabetes technologies into hospitals or into primary care practices will require healthcare professionals to restructure their treatment and workflow protocols to streamline data downloading, data interpretation and patient follow-up.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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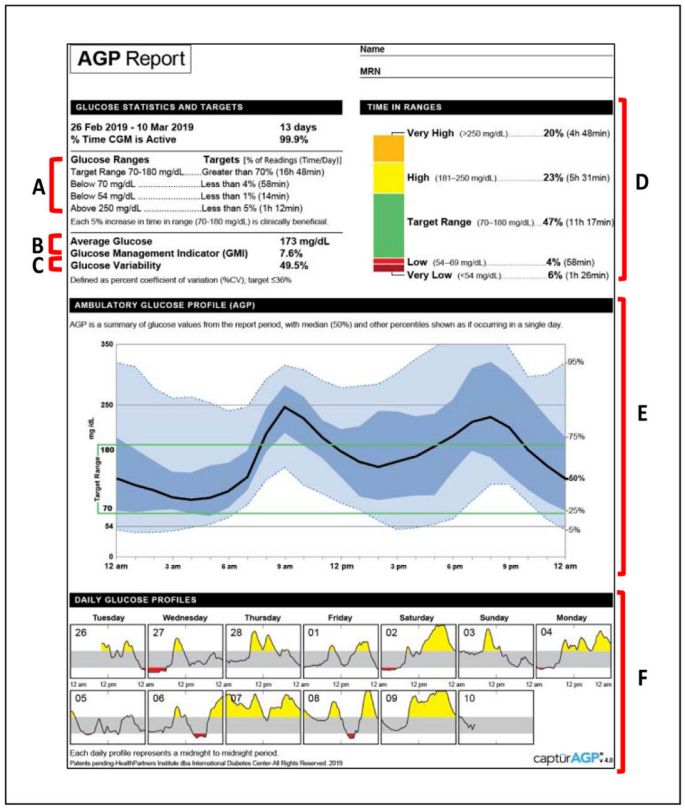
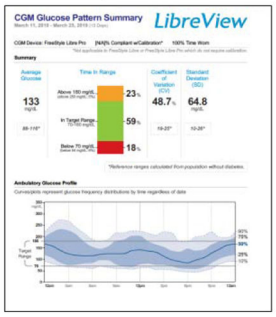


FreeStyle Libre View



Dexcom Clarity

Elements of the AGP

- The AGP displays the percentages of time within, above and below target range (**A**), average glucose, Glucose Management Indicator (GMI) (**B**) and glycemic variability, which is reported as the percentage of coefficient of variation (%CV) (**C**).
- The percentages in ranges are also presented graphically (**D**).
  - The High Hyperglycemia (Level 1) and Very High Hyperglycemia (Level 2) indicate percentage of time in TAR for each of the high glucose levels.
  - The Target Range indicates %TIR within patient's target glucose range.
  - Low Hypoglycemia (Level 1) and Very Low Hypoglycemia (Level 2) indicate percentage of time in range (TBR) for each of the low glucose levels.
- The Ambulatory Glucose Profile (AGP) combines daily profiles to create a one-day (24-hour) graphic (**E**).
  - The black line indicates the median glucose level at all day parts.
  - The dark and light blue shaded areas graphically depict the degree of glycemic variability (SD or %CV),
- The Daily Glucose Profiles present a glucose profile for each day covered (**F**).

Figure 1.
Ambulatory Glucose Profile (AGP)

Table 1.

Key features of current personal CGM systems

Feature	FreeStyle Libre 2	Dexcom G6	Medtronic Guardian Connect	Eversense
Indication, years of age	≥4	≥2	≥7	≥18
Sensor wear, days	14	10	7	90 (US), 180 (Europe)
Requires fingerstick test calibration	no	no	2 x/day	2x/day
Warm up period (hrs)	1	2	2	24 (upon insertion of the sensor) *
Requires confirmatory fingerstick test for insulin dosing	no	no	yes	no
Active alarms/alerts	yes	yes	yes	yes
Real-time remote monitoring (data sharing)	yes	yes	yes	yes
Connects with insulin pump	no	yes	yes	no
Accuracy: Overall' MARD, %	9.3 [28]	9.0[29]	10.4[30]	9.0[31]
Chemical substances Interferences	Ascorbic Acid; Salicylic Acid [32]	Hydroxyurea; [29] repeated doses of APAP [33]	Acetaminophen; Ethanol/ Wine; Albuterol; Lisinopril; Atenolol; Atorvastatin; Ascorbic Acid [34]	Tetracycline; Mannitol [35]
Interferences from Radiological Studies	Limited evidence of in-vitro exposure to X-Ray and RT, CT or MRI did not impact the data recorded by Libre Pro in 10 sensors [36]	No impact from X-Ray, CT or angiography among hospitalized patients (n=49); [37] there is some migration from MRI [38]	Medtronic recommends that users remove the sensor in the presence of X-ray, CT, MRI PET, Airport scanners [39]	Close contact with direct electromagnetic interference (EMI) may interfere with the smart transmitter's ability to send data to the mobile device. [40]

* The U.S. Food & Drug Administration cautions that readings from the first 12 hours of use should not form the basis of treatment decisions.

MARD : Mean Absolute Relative Difference

Table 2.

CGM Metrics for Use in Clinical Care

1. Number of Days CGM Worn (recommend 14 days) [75, 76]	
2. Percentage of time CGM is active (recommend 70% of data from 14 days)	
3. Mean Glucose	
4. Glucose Management Indicator (GMI) [77]	
5. Glycemic Variability (%CV) Target ≤36% [78]	
6. Time Above Range (TAR) - % of readings and time >250 mg/dL (>13.9 mmol/L)	Level 2
7. Time Above Range (TAR) - % of readings and time 181–250 mg/dL (10.1–13.9 mmol/L)	Level 1
8. Time In Range (TIR) - % of readings and time 70–180 mg/dL (3.9–10.0 mmol/L)	In Range
9. Time Below Range (TBR) - % of readings and time 54–69 mg/dL (3.0–3.8 mmol/L)	Level 1
10. Time Below Range (TBR) - % of readings and time <54 mg/dL (<3.0 mmol/L)	Level 2

Table 3.

Correlation between TIR and HbA1c [79, 80]

TIR 70–180 mg/dL (3.9–10.0 mmol/L)	**Estimated A1C % (mmol/mol)**	**TIR 70–180 mg/dL (3.9–10.0 mmol/L)**	**Estimated A1C % (mmol/mol)**
20%	9.4 (79)	20%	10.6 (92)
30%	8.9 (74)	30%	9.8 (84)
40%	8.4 (68)	40%	9.0 (75)
50%	7.9 (63)	50%	8.3 (67)
60%	7.4 (57)	60%	7.5 (59)
70%	7.0 (53)	70%	6.7 (50)
80%	6.5 (48)	80%	5.9 (42)
90%	6.0 (42)	90%	5.1 (32)
Every 10% increase in TIR = ~0.5% (5.5) A1C reduction		***Every 10% increase in TIR = ~0.8% (8.7) A1C reduction***	

Table 4.

Targets for assessment of glycemic control: Type 1 / Type 2 and Older/High-Risk Individuals [74]

Diabetes Group	Time in Range (TIR)		Time Below Range (TBR)		Time Above Range (TAR)	
	Within Target Range	% of readings time/day	Below Target Level	% of readings time/day	Above Target Level	% of readings time/day
Type 1 * / Type 2	70–180 mg/dL 3.9–10 mmol/L	>70% >16hr, 48 min	<70 mg/dL <3.9 mmol/L	<4% <1 hr	>180 mg/dL >10 mmol/L	<25% <6 hr
			<54 mg/dL <3.0 mmol/L	<1% <15 min	>250 mg/dL >13.9 mmol/L	<5% <1 hr, 12 min
Older/High-Risk	70–180 mg/dL	>50%	<70 mg/dL	<1%	>250 mg/dL	<10%
Type 1 / Type 2	3.9–10 mmol/L	>12 hr	<3.9 mmol/L	<15 min	>13.9 mmol/L	<2 hr, 24 min

* For age <25 yr., if the A1C goal is 7.5% then set TIR target to approximately 60%.

Table 5.

CGM Data Interpretation Process

Step 1	Confirm that sufficient CGM data are available for analysis. A minimum of 14 days of CGM use, covering at least 70% (10 days), is needed for accurate interpretation.
Step 2	Evaluate the average glucose and Glucose Management Indicator (GMI) and then review the TIR, TBR and TAR statistics.
Step 3	Pattern identification, focusing first on indicators of hypoglycemia. If the data show problematic time below range, it is important to formulate strategies to resolve this issue (e.g., adjust medication, modify health behaviors) before addressing any other concerns. The 24-hour glucose profile will show the time(s) when hypoglycemia is occurring. If a pattern exists, it may be necessary to review multiple days to identify any particular day(s) or time (s) when the patterns are most significant.
Step 4	Pattern identification, addressing hyperglycemia. If the data indicate that time in range is not at the desired target level, clinicians are advised to review the 24- hour glucose profile to identify the time(s) when hyperglycemia is occurring. This is particularly important when the standard deviation is elevated. If a pattern exists, it may be necessary to review multiple days to identify any particular day(s) when the patterns are most significant.
Step 5	Assess the basal insulin dose (if applicable). For patients treated with intensive insulin regimens, clinicians are advised to determine the appropriateness of the basal dose. It is also important that clinicians talk to patients to determine how they are dosing for meals and correcting for elevated glucose values.