Continuous Blood Glucose Monitoring: Is There a Proven Benefit?

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The CDC reports that there are about 1.2 million Americans with Type 1 diabetes mellitus (T1DM) and at least 1.75 million Americans with Type 2 diabetes mellitus (T2DM) that self-inject bolus insulin several times a day. According to the ADA, individuals that benefit from checking their blood glucose (BG) levels include patients taking insulin, pregnant patients, patients having a hard time controlling BG levels, patients with low BG (especially without the usual warning signs), and those who have ketones from high BG levels. Major clinical trials of insulin-treated patients have included self-monitoring of blood glucose (SMBG) in order to demonstrate the benefit of intensive glycemic control in preventing diabetes complications. According to the CDC, from 1994 to 2010, the percentage of diabetic adults performing daily SMBG increased from 35.7% to 63.6%, highlighting the major role that diabetic adults performing daily SMBG increased from 35.7% to 63.6%, highlighting the major role that SMBG plays in the management of diabetes.

Continuous blood glucose monitoring (CGM), however, may offer even more advantages to traditional self-monitoring of blood glucose by providing real-time information on high/low glucose patterns, directions, and rate of glucose changes, and hypo/hyperglycemia alerts. With the rapid advancement of diabetes-focused technologies, the days of painful fingertips to measure blood sugar levels may soon come to an end. The 2019 ADA guidelines suggest that, when used properly, CGM in conjunction with intensive insulin regimens is a useful tool to lowering glycosylated hemoglobin (A1C) in adults with diabetes who are not meeting glycemic targets.

Methods of Checking Blood Glucose

Traditional glucose monitoring using the fingerstick method is used by most diabetic patients. The fingerstick method is useful in that it shows changes in BG quickly when patients’ glucose levels are rapidly increasing or decreasing (i.e., post-prandial or after exercise). However, constantly using the fingerstick method as a means to check blood glucose may cause the skin on patients’ fingers to become thick and callused, making it
more painful. Patients who have difficulty obtaining blood from their finger have opted for newer glucose monitoring methods from alternative locations. The term alternative site testing (AST) means the parts of the body other than the fingers to obtain BG level. For instance, venous blood drawn from the forearm or the use of CGM sensors are alternative methods that patients can use. Although these newer options may be appealing to some patients, there has not been enough discussion about whether or not these alternative sites will mimic the results obtained from the fingerstick.

Chopra et al conducted a clinical study that analyzed the correlation of glucose levels between venous blood and fingerstick blood samples in patients with T1DM or T2DM. They found that the mean random BG levels in the fingerstick group and the venous blood control group were 206.67 mg/dL and 194.49 mg/dL, respectively. The study also showed that 68.57% of fingerstick BG readings were within 15% of the venous BG readings. Rather than measuring glucose levels from your blood, CGM readings are taken from the interstitial fluid (ISF), a thin layer of fluid that surrounds the cells of the tissues below the skin. Blood glucose readings from the fingerstick and forearm tend to be about 5 minutes ahead of interstitial glucose readings. Basu et al performed the first direct measurement of this phenomenon in eight healthy subjects under an overnight fasted condition. In the study, microdialysis catheters were inserted into the abdominal subcutaneous space of the participants. After IV bolus administrations of glucose tracers, samples of plasma and ISF were collected and analyzed. The study results showed that the mean lag time of tracer appearance in the interstitial space was 5.3–6.2 minutes. The study concluded that in the overnight fasted state in healthy adults, the physiological delay of glucose transport from the blood vessels into the interstitial space is 5–6 minutes. These results show that using the traditional fingerstick method can allow for a faster and more accurate BG measurement compared to using interstitial fluid. However, CGM devices may provide some benefit in real-world settings as they are able to capture daily glucose trends and alert patients that tend to be unaware of their hypoglycemia or hyperglycemia. Health care providers should consider counseling their patients on the fact that blood glucose readings may differ with the alternative testing sites, and develop a glucose monitoring plan with their patients in order to minimize any risk associated with alternative site testing.

**Clinical Trials**

**T1DM**

Aleppo et al conducted a randomized, noninferiority, clinical trial to determine whether the use of CGM without confirmatory SMBG measurements is as safe and effective as using CGM with SMBG in adults with well-controlled T1DM. The study was conducted at 14 sites in the T1DM Exchange Clinic Network in the United States. To be included in the study, participants had to be at least 18 years of age, had T1DM for at least one year, had current use of an insulin pump, and had an A1C of 9.0% or less. Exclusion criteria included: severe hypoglycemia (defined as the occurrence of a severe hypoglycemic event resulting in seizure or loss of consciousness in the past 3 years, or requiring the assistance of another individual in the past 12 months), significant hypoglycemia unawareness, more than one diabetic ketoacidosis (DKA) event in the past year, history of seizures other than due to hypoglycemia, current use of a threshold suspend pump feature, myocardial infarction or stroke in past 6 months, eGFR < 30 within the prior 12 months, abnormal thyroid function test, presence of a significant medical or psychiatric disorder, cognitive difficulties, initiation of a non-insulin drug for glucose control during the past 3 months, use of a systemic beta blocker drug, regular use of oral corticosteroids, anticipated acetaminophen used during study (due to the interaction noted between APAP use and CGM devices), inpatient psychiatric treatment in the past 6 months, currently pregnant/lactating or planning to attempt pregnancy, participation in an intervention study in past 6 weeks, known adverse allergy, CGM values <60 mg/dL for more than 10.0% of the time, and an unsuccessful completion of the run-in phases with respect to CGM or SMBG use.

A total of 226 patients were enrolled and randomly assigned at a 2:1 ratio to either the CGM-only (n = 149) or CGM+SMBG (n = 77) group based on a permuted block design with stratification by clinical site. The CGM-only group used the Dexcom™ G4 Platinum™ System with modified algorithm, whereas the CGM+ SMBG used the Dexcom™ G4 Platinum™ CGM System with modified algorithm in addition to the Abbott™ Precision Xtra™ Blood Glucose-Ketone Meter. After randomization, participants in both groups were instructed to calibrate the study CGM per Dexcom™ specifications and to use it daily. Both groups also were instructed to perform a SMBG measurement when the fasting CGM glucose concentration was >300 mg/dL or when the CGM glucose concentration during the day was >300 mg/dL for 1 hour. The CGM+SMBG group was also instructed to perform a SMBG measurement with the study meter for CGM calibrations whenever an insulin bolus was administered, when treating or attempting to prevent hypoglycemia, and before going to bed. On the other hand, the CGM-only group was instructed to dose insulin and make management decisions on the basis of the CGM sensor glucose concentration itself, except in the following circumstances that required SMBG testing: 1) 12 h after insertion of a new sensor, 2) on a sick day (e.g., nausea, vomiting), 3) 4 h after taking acetaminophen, 4) symptoms suggestive of hypoglycemia but the CGM sensor glucose concentration was not hypoglycemic or dropping rapidly, 5) 20 min after treating a low CGM sensor glucose concentration if the CGM sensor glucose level had not begun to rise, 6) before administering an insulin bolus when the CGM sensor glucose concentration was >250 mg/dL, and 7) fasting CGM glucose >300mg/dL or CGM glucose concentration during the day >300 mg/dL for 1 h in length. If a CGM calibration measurement coincided with a meal, the participant was instructed to base the meal bolus on the CGM sensor value and then perform SMBG measurement to calibrate the CGM. The primary outcome was time in range (70–180 mg/dL) over the 26-week trial, with a prespecified noninferiority limit of 7.5%.

For the primary outcome of CGM-measured time in the glucose range of 70–180 mg/dL, CGM use alone was shown to be non-inferior to using CGM and SMBG together. The mean time spent in the range of 70–180mg/dL was 63% at both baseline and 26 weeks in the CGM-only group, and 65% at both baseline and 26 weeks in the CGM+SMBG group. AIC was measured at baseline, 13 weeks, and 26 weeks at the Northwest Lapid Research Laboratories. The mean AIC was 7.1% at baseline and 26 weeks for the CGM only group, compared to 7.0% at baseline and at 26 weeks in the CGM+SMBG group. Mean change in A1C from baseline was 0.0% for each group (p = 0.41). No severe hypoglycemic events occurred in the CGM-only group, while one...
Table 1 | Summary of Clinical Trials\textsuperscript{10,11}

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<tr>
<th>Study</th>
<th>Comparator Groups</th>
<th>Primary Endpoint</th>
<th>Results</th>
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| Alejandro G et al. (2017)\textsuperscript{10} | CGM\textsuperscript{a} vs CGM+SMBG\textsuperscript{b} | Mean % time in range 70–180 mg/dL | At Baseline  
  CGM: 63% ± 13%  
  CMG+SMBG: 63% ± 13%  | Adjusted Difference 0%  
 (one-sided 95% CI -2%).  |
| Haak T et al. (2017)\textsuperscript{11} | CGM vs SMBG | Difference in A1C at 6 months | CGM: -0.29%  
  SMBG: -0.31%  | 0.03 (± 0.114); p = 0.8222 |

\textsuperscript{a} Continuous glucose monitoring; \textsuperscript{b} Self-monitoring of blood glucose; \textsuperscript{c} Confidence Interval

**T2DM**

Haak et al conducted a multicenter open-label RCT, known as the REPLACE trial, in order to assess the safety and efficacy of new flash glucose-sensing technology to replace SMBG in T2DM patients.\textsuperscript{11} The SMBG group used a standard FreeStyle™ device, while the CGM group used a novel sensor-based flash glucose monitoring system known as the FreeStyle Libre™. Flash Glucose Monitoring (FGM) is the newest method of glucose testing seen as a hybrid between meters and CGMs in that they have an arm sensor in addition to a separate touchscreen reader device. When the reader device is swiped close to the sensor, the sensor transmits both an instantaneous glucose level and eight-hour trend graph to the reader.\textsuperscript{14} The Haak et al trial was 6 months in duration and was located across 26 European diabetes centers: eight in France, ten in Germany, and eight in the UK.

The study enrolled patients 18 years or older with T2DM treated with insulin for at least 6 months and on their current regimen (prandial only, prandial and basal intensive insulin therapy, or continuous subcutaneous insulin infusion [CSII] therapy) for 3 months or more, had an A1C level between 7.5–12.0%, self-reported regular blood glucose testing (more than 10/week for at least 2 months prior to study entry), and were considered by the investigator to be technically capable of using the flash sensor-based glucose monitoring system. Exclusion criteria included patients on any other insulin regimen that was not described in the inclusion criteria, patients with total daily dose of insulin of 1.75 units/kg or greater, had severe hypoglycemia (requiring third-party assistance), DKA, or hyperosmolar-hyperglycemic state in the preceding 6 months; known allergy to medical-grade adhesives; used CGM within the previous 4 months; were pregnant or planning pregnancy; were receiving steroid therapy for any condition; or were considered by the investigator to be unsuitable to participate.\textsuperscript{11}

A total of 224 subjects were randomized and 201 completed the study. Participants were centrally randomized in a 2:1 ratio to the FreeStyle Libre™ CGM (intervention group) or to a standard FreeStyle™ SMBG device (control group). No training was provided to the CGM participants for interpretation of glucose sensor data. Their historical data was uploaded at subsequent study visits and glucose reports were generated for review by the HCP with the participant, using the device software. Control participants self-managed their glucose levels using a standard blood glucose device and a glucose diary for the duration of the study, wearing a blinded sensor for the last 2 weeks of the study. Both the intervention and control patients had two doctor visits. At these visits, participants’ glucose control was reviewed with a HCP and the effects of diet/lifestyle on glucose trends and insulin dose modifications were discussed. A1C was measured in all participants at baseline and at 3 and 6 months with analysis by a central laboratory. SMBG frequency for control participants was 3.9 ± 1.5 test/day (median 3.9) at baseline and this rate was maintained until study end [3.8 ± 1.9 (median 3.9)]. The primary outcome was the difference in A1C between intervention and control groups at 6 months.\textsuperscript{11}

There was no statically significant difference in A1C change at 6 months between the CGM and SMBG group [-0.29% vs -0.31%, mean difference 0.03 (± 0.114); p = 0.8222]. In terms of secondary outcomes, time in hypoglycemia (defined as BG <70 mg/dL) reduced by 43% (-0.47 ± 0.13 h/day) for CGM participants compared with SMBG (p = 0.0006). Time in hypoglycemia (defined as BG <55 mg/dL) reduced by 53% (-0.22 ± 0.068 h/day) for CGM participants compared with SMBG (p = 0.0014). The mean amplitude of glycemic excursion (MAGE) was also compared between the two treatment groups. At the completion of the study, MAGE decreased for the CGM group from baseline (from 125 to 125 mg/dL respectively), but MAGE remained unchanged for the SMBG group (131 mg/dL). The mean difference was -4 (±3.3, p<0.1909).\textsuperscript{11}
This European study is the first to investigate the use of flash sensor-based glucose technology as a replacement for standard SMBG in individuals with T2DM treated with intensive insulin therapy. The trial concluded that CGM use in T2DM with intensive insulin therapy results in no difference in A1C change and reduced hypoglycemia compared to SMBG, thus offering a safe, effective replacement for SMBG. When compared with SMBG testing, there were no safety concerns with CGM use. Based on the p values mentioned, the CGM device was associated with statistically significant reductions in hypoglycemic measures across all age groups, decreased glucose variability, and improved quality of life and treatment measures. Even though the primary endpoint was not achieved (no statically significant difference in A1C change at 6 months compared to SMBG), the secondary endpoints do demonstrate the safety aspect of CGM compared to standard SMBG, which led to the FDA approval of this CGM device.11

### Adverse Effects and Precautions

The CGM devices appear to be well tolerated, with the most common adverse effects (>10%) being hypersensitivity reactions, itching, pain, redness, burning, and subcutaneous hemorrhage at the application site, sleep disturbances, and attention deficits. Some patients also experienced problems related to the CGM monitor, the adhesive tape, and the sensor. Hypoglycemia can occur from using this device, but CGM has been shown to cause less hypoglycemia than SMBG in the clinical trials mentioned.5,10

In the Aleppo et al trial, no occurrences of DKA occurred in either group. There were no deaths in either treatment arm, but 4 participants suffered from serious adverse effects in both groups (CGM group: tachycardia, MI, Basedow’s disease, and squamous cell carcinoma; CGM+ SMBG group: injury, hypoglycemic seizure, nephrolithiasis, and knee arthroplasty). There were no serious adverse events or severe hypoglycemic events reported related to sensor data use in the Haak et al study. However, six participants of the CGM group reported a total of nine adverse events for sensor-wear reactions (two severe, six moderate, one mild).11 Overall, more studies need to be conducted as newer versions of the CGM devices are being approved in the market.

### Clinical Features

As of July 2018, the FDA approved four continuous glucose monitors: Dexcom’s G6™ System, Abbott’s™ Freestyle Libre™ 14 Day Flash Glucose Monitoring System, the Eversense™ Continuous Glucose Monitoring System, and the Guardian Connect™ System. These CGMs require three parts: Sensor, Transmitter, and a smartphone/receiver. Due to variable adherence, optimal CGM use requires an assessment of individual readiness for the technology as well as initial and ongoing education and support. Two of the CGM devices are now approved by the FDA for making treatment decisions without SMBG confirmation: Dexcom’s G6™ and Abbott’s™ Freestyle Libre™ CGM devices. The other two systems have the potential to reduce the number of fingersticks from 3-4 times a day to only two a day. Out of the 4 CGM devices approved by the FDA, only Dexcom’s™ G6™ and Abbott’s™ FreeStyle Libre™ CGM devices are covered by Medicare at this time.

### Table 2 | Common Adverse Effects of CGM* from Clinical Trials5,10

<table>
<thead>
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<tr>
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*Continuous glucose monitoring

### Dexcom™ G6™ System

In March 2018, the FDA approved Dexcom’s G6™ model CGM. The G6 is an upgrade from the G5™ model because it requires no fingersticks for calibration and the sensors last 10 days. Dexcom’s G6™ is unique in that it can be integrated into insulin pumps and it can predict hypoglycemic and hyperglycemic trends. This was the first FDA-approved CGM system that could be used to make diabetes treatment decisions without confirmation from the traditional fingerstick test.16

### Abbott’s™ Freestyle Libre™ 14 Day Flash Glucose Monitoring System

In September 2017, the FDA approved a second CGM that did not require fingersticks, known as the FreeStyle Libre™ CGM from Abbott™ Laboratories. The U.S. version of the Libre does not allow transmission alerts to smartphones, but patients are able to view their glucose readings on a small handheld device passed over the sensor, which is placed on the upper arm. The new and improved 14-day sensor allows patients to have a full 2 weeks before the sensor has to be changed.16

### Eversense™ Continuous Glucose Monitoring System

In June of 2018, Eversense™ was approved by the FDA by Senseonics, Inc. This device is unique in that it monitors blood glucose for 90 days via an under-the-skin sensor, a removable and rechargeable smart transmitter, and an app for real-time diabetes monitoring and management. The Eversense™ mobile app can alert the user to low and high sensor glucose values based on alert settings programmed by the user. Patients can also enter blood glucose measurements, meals, exercise, and insulin dosing. This device requires confirmation from the traditional fingerstick test.16

### Guardian Connect™ System

In March 2018, the FDA approved Medtronic’s™ first standalone CGM, Guardian Connect™. The system works with sensors worn on the upper arm or abdomen. The sensors last up to 7 days. The Guardian Connect™ predicts where blood sugar levels are headed and alerts the person 10 minutes to an hour before a high or low level occurs. Guardian Connect™ requires two fingersticks per day to calibrate the system. This device also requires confirmation from the traditional fingerstick test.16
**Clinical Implications**

Results from the clinical trials mentioned above have shown that the use of CGM compared with usual care resulted in lower A1C levels or greater mean time in therapeutic range for diabetes not meeting A1C targets. Furthermore, the use of CGM devices in T2DM patients reduced hypoglycemia compared to SMBG, thus offering a safe, effective replacement for SMBG. The Haak et al study is one of the only clinical trials with real-world application to the T2DM population, which is notable since many T2DM patients express pain and unwillingness to perform multiple fingersticks daily. There appears to be limited studies on the use of CGM in diabetic patients, and many of the studies that do exist used CGM along with confirmatory SMBG.

CGM devices may be particularly useful in insulin-treated patients with hypoglycemia and reducing frequent hypoglycemic episodes, however, evidence is lacking on the use of CGM devices in non-insulin treated patients. Many of the studies also excluded individuals with significant hypoglycemia unawareness, and gave instructions to the participants to use traditional SMBG at these times. This emphasizes the need for future studies to assess the safety of CGM in less compliant adults, such as patients with higher A1C levels who perform SMBG testing fewer than four times a day, and patients with hypoglycemia unawareness. Furthermore, due to the prevalence of T1DM in children, it is important to assess the safety of CGM in the youth as well as well as identify barriers to the effectiveness of CGM in children and young adults. Tamborlane et al conducted a multicenter RCT back in 2008 to determine the efficacy and safety of CGM in adults and children with T1DM. This trial is one of the few that has shown promising results of CGM use in patients under the age of 18, however further study in this population is warranted, especially with the newly approved CGM devices. Lastly, there has been an interaction noted between APAP and CGM devices. It is important that healthcare providers counsel patients on the use of APAP when using CGM. Clinicians may need to counsel patients on using fingersticks at times when APAP therapy is warranted or advise patients to use alternative pain management therapies if appropriate. Fortunately, CGM manufacturers have made efforts to reduce the susceptibility of CGM sensors to APAP interference by either changing the working voltage of the sensor or by applying a more perme-selective membrane to the sensor surface. Therefore, this pharmacological interaction should not be as much of a concern when using the newer generation of CGM devices. Overall, the studies mentioned above were relatively short in duration compared to the lifelong duration of this disease in patients, therefore it is difficult to determine if the results seen would be maintained over years with use of CGM.

**Conclusion**

In conclusion, CGM use has showed no statistically significant reduction in A1C, but has shown some benefit in reducing the number of daily fingersticks and the time in hypoglycemia when compared to SMBG alone. CGM may be beneficial for patients unwilling to use SMBG, however, long term RCTs are warranted in order to support this conclusion. Novel CGM devices provide patients with easy access to data about trends in their BG levels throughout the day, which can assist in targeted therapy changes. Postprandial hyperglycemia and asymptomatic nocturnal hypoglycemia are commonly seen in diabetic patients, so CGM use can assist these patients in analyzing fluctuations in their glucose levels. In addition, there is a cost-benefit seen with CGM use. According to the ADA, for patients testing their BG 6 times/day, CGM saves over $120 per person per month (PPPM) compared with SMBG, and for people testing more than 3 times/day, CGM has a lower acquisition cost than SMBG. With this new method of BG monitoring likely growing in the future, it is important for both patients and health care providers to gain a better understanding of how to ensure favorable health outcomes when using CGM devices. Therefore, it is imperative that clinicians provide in-depth diabetes education, training, and support, for optimal CGM implementation and ongoing use in the future.

**References**

Using Pharmacogenetic Testing to Guide Antidepressant Selection: A Patient Case

The UF Health Precision Medicine Program (PMP) offers clinical support for CYP2C19 and CYP2D6 genotyping in patients initiating therapy with selective serotonin reuptake inhibitors (SSRIs) or in those who are not responding to these agents as expected. SSRIs are deactivated by multiple drug metabolizing enzymes, including CYP2C19 and CYP2D6.

Clinical pharmacogenetic guidelines recommend a 50% dose decrease or alternative therapy for CYP2C19 and/or CYP2D6 poor metabolizers when prescribed SSRIs with a significant drug-gene interaction. Alternative therapy is also recommended for CYP2C19 rapid or ultrarapid and/or CYP2D6 ultrarapid metabolizers when a significant drug-gene interaction exists.¹

Patient Presentation

A 66 year-old female with a history of treatment-resistant major depressive disorder and anxiety presented to the UF Health Pharmacogenetics consult service at Internal Medicine – Tower Hill for a consult. She reported insomnia, memory loss, and suicidal ideation, with sleep and mood being her primary complaints. The patient has previously tried and failed nortriptyline, bupropion, olanzapine, vortioxetine, aripiprazole, duloxetine, buspirone, and sertraline. Current medications include fluoxetine and diazepam.

Pharmacogenetic Test Results

CYP2C19*1/*1; Normal metabolizer phenotype (Normal CYP2C19 activity)
CYP2D6*4/*4; Poor metabolizer phenotype (No CYP2D6 activity)

Drug Therapy Recommendations

Although her CYP2C19 function is normal, this patient’s CYP2D6 poor metabolizer phenotype increases her risk of having increased side effects with SSRIs metabolized by CYP2D6, including paroxetine, fluvoxamine, and potentially fluoxetine. Evidence is weaker for fluoxetine and multiple metabolic pathways exist for this agent. However, its metabolism includes CYP2D6 and adverse effects could be increased in CYP2D6 poor metabolizers.

Based on this patient’s CYP2D6 genotype, worsening insomnia with fluoxetine, and the potential for increased levels of fluoxetine, we recommended switching to a non-CYP2D6 SSRI such as escitalopram, citalopram, or sertraline, with dose titration and monitoring. A direct switch to escitalopram was recommended first line since the patient had previously tried and not responded to sertraline. Having pharmacogenetic information available when choosing or titrating antidepressant therapy can help decrease the risk for side effects and increase the likelihood of a positive response in selected patients.²

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