Advantages and Disadvantages of Realtime Continuous Glucose Monitoring in People with Type 2 Diabetes

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Abstract
Previous research has shown that realtime continuous glucose monitoring (RT-CGM) is a useful clinical and lifestyle aid for people with type 1 diabetes. However, its usefulness and efficacy for people with type 2 diabetes is less known and potentially controversial, given the continuing controversy over the efficacy of self-monitoring of blood glucose (SMBG) in this cohort. This article reviews the extant literature on RT-CGM for people with type 2 diabetes, and enumerates several of the advantages and disadvantages of this technology from the perspective of providers and patients. Even patients with type 2 diabetes who are not using insulin and/or are relatively well controlled on oral medications have been shown to spend a significant amount of time each day in hyperglycemia. Additional tools beyond SMBG are necessary to enable providers and patients to clearly grasp and manage the frequency and amplitude of glucose excursions in people with type 2 diabetes who are not on insulin. While SMBG is useful for measuring blood glucose levels, patients do not regularly check and SMBG does not enable many to adequately manage blood glucose levels or capture marked and sustained hyperglycemic excursions. RT-CGM systems, valuable diabetes management tools for people with type 1 diabetes or insulin-treated type 2 diabetes, have recently been used in type 2 diabetes patients. The extant studies, although few, have demonstrated that the use of RT-CGM has empowered people with type 2 diabetes to improve their glycemic control by making and sustaining healthy lifestyle choices.

Keywords
Type 2 diabetes, realtime continuous glucose monitoring systems, advantages and disadvantages

Realtime continuous glucose monitoring (RT-CGM), which provides a glucose reading and trend every five minutes for up to seven days, is a valuable diabetes management tool for people with type 1 diabetes who, in their quest for tight glycemic control, are particularly vulnerable to severe and potentially life-threatening hypoglycemia. The value of RT-CGM for people with type 2 diabetes is less well recognized, particularly for those who are non-insulin treated. This paper reviews the still nascent literature documenting the efficacy of RT-CGM in people with type 2 diabetes and then addresses the advantages and disadvantages of its use from the perspectives of the healthcare provider and the patient.

Previous Studies Documenting Efficacy of Realtime Continuous Glucose Monitoring in People with Type 2 Diabetes
The few studies that have examined the clinical efficacy of RT-CGM in people with type 2 diabetes are shown in Table 1. These studies show that RT-CGM may be useful in modifying lifestyle habits and choices and can exert a positive effect for as long as a year beyond the intervention. Using an RT-CGM system as a ‘motivational device’, Yoo et al. conducted a prospective, open-label, randomized controlled trial (RCT) of RT-CGM compared with self-monitoring of blood glucose (SMBG) in 65 adult patients with poorly controlled type 2 diabetes (8.0 % ≤ glycated hemoglobin [HbA1c] ≤10 %) over a three-month period. The intervention group used the RT-CGM device for three days each month for three months and the control group continued SMBG at least four times a week for three months. Compared with the SMBG group, the RT-CGM group demonstrated a more significant reduction in HbA1c (-1.1 % versus -0.4 %), a larger increase in the exercise time per week (+158 minutes versus +43 minutes), and a more pronounced trend toward a decrease in body weight (-2.2 kg versus -1.4 kg). The researchers also measured the mean amplitude of glucose excursion (MAGE) with each RT-CGM application; there was a statistically significant decrease in MAGE between Month 1 and Months 2 and 3. Vigersky et al. conducted a prospective, 52-week, two-arm RCT comparing RT-CGM (n=50) versus SMBG (n=50) in people with type 2 diabetes, showing...
diabetes not using prandial insulin. This is the largest study in patients with type 2 diabetes to date. The RT-CGM device was used for four three-week cycles (two weeks on/one week off). Subjects randomized to RT-CGM were asked to perform SMBG to calibrate the RT-CGM device as directed by the manufacturer in order to confirm the RT-CGM values before each meal, at bedtime, and for all episodes of hypoglycemia (<70 mg/dl) or hyperglycemia (>180 mg/dl). Patients randomized to SMBG were asked to perform SMBG before each meal and at bedtime. All patients were managed by their usual provider and were instructed to contact their primary care provider for all treatment decisions; there was no therapeutic intervention by the study team.

The intention-to-treat analysis of the data showed that RT-CGM significantly reduced HbA1c compared with SMBG alone during the time of its use (-1.1 versus -0.5 %) and the HbA1c reduction was sustained for the following 40 weeks (-0.8 versus -0.2 %). In a per protocol analysis of the data comparing those who used the RT-CGM device for >48 days versus those who used it for ≤48 days (the maximum possible use was 56 days), the HbA1c differences were even greater at 12 weeks (-1.3 versus -0.6 %) and at 52 weeks (-1.0 versus -0.2 %). There was a significant reduction in weight during the first 12 weeks as well. Although not statistically significant, the trend toward weight loss in the RT-CGM group persisted for the remaining 40 weeks.

A recent health economics analysis based on the findings from the study by Fonda et al. showed that, due to its favorable relationship with glycemic control, RT-CGM was a cost-effective intervention for this cohort. Specifically, if healthcare providers were to offer RT-CGM as was done in the Vigersky et al. study, it would result in an incremental cost of $250. The incremental cost-effectiveness ratios are $2,903 per life-year gained and $3,735 per QALY gained. If healthcare providers were to offer RT-CGM again one year later as a ‘refresher’, there would be a greater QALY gain (0.165 or two months) at an incremental cost of $1,217, with a cost-effectiveness ratio of $10,071 per QALY gained. These costs are substantially below the threshold separating cost-effective interventions from costly interventions.3

Garg et al. studied 91 insulin-requiring patients with type 1 diabetes (n=75) and type 2 diabetes (n=16) who wore a masked continuous glucose monitoring (CGM) device for three consecutive 72-hour periods. Subjects were randomly assigned to either a control group (continuous glucose data masked) or a display group (continuous glucose data displayed) during Period 1, but displayed during Periods 2 and 3. Compared with the control group, the display group spent 21 % less time in hypoglycemia (<55 mg/dl), 23 % less time in hyperglycemia (>141 mg/dl), and 26 % more time in the target range (81–140 mg/dl). Nocturnal hypoglycemia was reduced by 38 % (<55 mg/dl) and 33 % (55–80 mg/dl) in the display group.4

### Table 1: Summary of the Studies Examining the Clinical Efficacy of Realtime Continuous Glucose Monitoring in People with Type 2 Diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Type of Diabetes</th>
<th>Treatment</th>
<th>Duration</th>
<th>Device</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garg et al., 2006</td>
<td>91</td>
<td>Type 1 diabetes: 75</td>
<td>Patients wore an RT-CGM device for three consecutive 72-hour periods.</td>
<td>Three</td>
<td>DexCom STS</td>
<td>The display group spent 21 % less time in hypoglycemia (&lt;55 mg/dl), 23 % less time in hyperglycemia (&gt;141 mg/dl), and 26 % more time in the target glucose range (81–140 mg/dl). Nocturnal hypoglycemia was reduced by 38 % (&lt;55 mg/dl) and 33 % (55–80 mg/dl) in the display group.</td>
</tr>
<tr>
<td>Viggersky et al., 2012</td>
<td>100</td>
<td>Type 2 diabetes not on prandial insulin</td>
<td>Patients spent 12 weeks intermittently wearing an RT-CGM device or performing SMBG and were followed for 40 weeks to look at long-term differences</td>
<td>12 weeks</td>
<td>DexCom SEVEN</td>
<td>Significant difference in HbA1c at the end of the active intervention that was still present during the follow-up period. Significantly greater decline in patients wearing the RT-CGM device than performing SMBG</td>
</tr>
<tr>
<td>Yoo et al., 2008</td>
<td>65</td>
<td>Type 2 diabetes with HbA1c between 8 and 10 %</td>
<td>The RT-CGM group wore an RT-CGM device for three days each month for three months. The SMBG group checked blood sugar at least four times a week for three months</td>
<td>12 weeks</td>
<td>Medtronic Guardian REAL-Time</td>
<td>Intermittent use of the RT-CGM device was superior to SMBG in reducing total calorie intake/day, increasing total exercise time/week, reducing body weight, reducing BMI, reducing post-prandial glucose, and lowering HbA1c after three months</td>
</tr>
<tr>
<td>Bailey et al., 2007</td>
<td>140</td>
<td>Type 1 diabetes: 109</td>
<td>This was an observational study in which participants wore an RT-CGM device for 12 weeks continuously. They were seen at three-week intervals to download data and HbA1c was measured at baseline, 6, and 12 weeks</td>
<td>12 weeks</td>
<td>DexCom STS</td>
<td>A reduction of HbA1c was observed in all patients irrespective of diabetes type and insulin status. The largest reduction was seen in patients whose HbA1c was above 9.0 % at baseline. Increased use of the RT-CGM device was associated with larger reductions in HbA1c</td>
</tr>
</tbody>
</table>

BMI = body mass index; CGM = continuous glucose monitoring; HbA1c = glycated hemoglobin; RT-CGM = realtime continuous glucose monitoring; SMBG = self-monitoring of blood glucose.
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blood glucose range by 16% (5.77 versus 6.69 hours; p<0.0001). Similar to Vigersky et al.’s study, these improvements were made without a prescribed regimen based on RT-CGM values, alerts, or alarms. The ability to warn patients with type 1 diabetes and insulin-treated type 2 diabetes of impending hypoglycemia is a significant benefit of RT-CGM, as is its ability to show patients immediate and durable effects of lifestyle choices—e.g., diet and physical activity.6

Bailey et al. found that the use of RT-CGM for 12 weeks reduced HbA1c (-0.6 ± 0.1 %; p<0.0001) in 30 patients with type 2 diabetes who were taking insulin and/or oral agents.5 However, there was no significant improvement in the seven patients using oral only agents.

Studies Showing Efficacy of Continuous Glucose Monitoring in People with Type 2 Diabetes

Fritschi et al. conducted a descriptive study that examined the experience of 35 women with type 2 diabetes wearing a masked CGM device for three days.6 Eighty-six percent of patients were surprised by their blood glucose values; specifically, they did not realize the values could go as high as 300 mg/dl. Ninety-four percent stated that the information they learned from the CGM device would positively change the way they took care of their diabetes, including a change of diet (60 %) and an increase in physical activity (34 %). Allen et al. assessed the effectiveness of two interventions, CGM and problem-solving skills compared with CGM counseling and general diabetes education, in a two-week pilot study involving 29 women with type 2 diabetes, a mean age of 53 years, a mean duration of diabetes of 6.7 years, and suboptimal glycemic control.7 The study showed the CGM and problem-solving intervention increased problem-solving skills with a subsequent improvement in diet, minutes of moderate physical activity, weight, and HbA1c.

Advantages of Realtime Continuous Glucose Monitoring—The Provider’s Perspective

Glycemic Variability

Glycemic variability is the degree of fluctuation around mean blood glucose levels. It has been hypothesized that a reduction in glycemic variability—-independent of HbA1c reduction—may decrease the number and severity of diabetes complications.8,9 One of the main advantages of RT-CGM over SMBG, from the provider’s perspective, is that it is a clinical tool that can aid in the identification (and treatment) of glycemic variability, which is becoming an important metric in providing a more complete view of glycemic control. Unfortunately, the amount of glucose data necessary to calculate accurate measures of glycemic variability is large and not likely to be provided consistently by all patients with type 2 diabetes using SMBG. RT-GM provides a relatively simple tool for this purpose, and most software supporting RT-CGM devices automatically calculates multiple measures of glycemic variability after data upload.

Glycemic variability may contribute to the development of diabetes complications via the production of oxidative stress.10 Work by Monnier et al. showed that increasing glycemic variability in patients with type 2 diabetes is strongly correlated with urinary excretion of iso-8 prostaglandin F2α (8-iso-PGF2α).11 Ceriello et al. investigated the relation between glucose variability, oxidative stress (assessed by plasma 3-nitrotyrosine and 24-hour excretion rates of free 8-iso-PGF2α), and endothelial function determined by flow-mediated dilatation in patients with type 2 diabetes and in healthy controls.12 Their results suggested that variable glucose levels have a more damaging effect on endothelial function and enhance oxidative stress more than consistently high glucose levels.

Several studies have related glycemic variability to adverse health outcomes including cognitive function, retinopathy, and cardiovascular disease. In a study of 248 older adults (65-85, mean 80.2 years) without a history of dementia and adjusted for education, diabetes duration, hypertension, coronary heart disease, and smoking history, Zhong et al. demonstrated a negative correlation between the standard deviation (SD) of glucose and the largest amplitude of glucose levels, and how patients scored in the Mini Mental Status Examination.13 The effect of glycemic variability on cognitive function was confirmed by Rizzo et al.,14 who showed that MAGE was strongly associated with impaired cognitive functioning independent of HbA1c fasting plasma glucose (FPG), and post-prandial glucose (PPG) among older type 2 diabetes patients (r=0.83; p<0.001).15

In a study examining the effect of glucose variability on retinopathy in patients with type 2 diabetes, Gimeno-Orna et al. retrospectively calculated the coefficient of variation of FPG in 130 patients without retinopathy at baseline with a mean follow-up of 5.2 years.16 The highest quartile of variation in FPG contributed to diabetic retinopathy independently from and in addition to HbA1c (odds ratio 3.68; p<0.049).

Su et al. examined the parameters of glucose profiles using 72-hour masked CGM in 344 type 2 diabetes patients with coronary artery disease (CAD), and established a correlation between glycemic variability and the severity of CAD assessed by coronary angiogram, using the Gensini score.17 Glycemic variability measures included the MAGE, the mean of daily differences (MODD), and the post-prandial glucose excursion (PPGE). Angiography was performed after patients completed CGM. Among the 344 participants, 252 had angiographically proven CAD and 92 had almost normal coronary arteries. There was no significant difference in the HbA1c and FPG levels between the two groups, but MAGE and PPGE were significantly higher in patients with CAD than in patients without. The Gensini score was closely related to MAGE (r=0.277, p<0.001), PPGE (r=0.167, p=0.002), and HbA1c (r=0.136, p<0.011) but not with MODD. A multivariate linear regression analysis model that explained 19.1 % of the variation in the Gensini score showed that MAGE (p<0.001) and HbA1c (p=0.022) were independent risk factors for the presence of CAD in type 2 diabetes patients.18

A recent review concluded that glucose variability in combination with HbA1c may be a more reliable indicator of glycemic control and provide greater insight into the risk of long-term diabetes complications than HbA1c alone.19 Findings from several studies using masked CGM or RT-CGM in patients with type 2 diabetes support the use of CGM systems as the best tool available at present that can adequately give healthcare providers information about their patients’ glycemic variability. In a three-day study using a masked CGM device to assess the prevalence of hyperglycemia throughout the day in men with relatively well controlled type 2 diabetes (HbA1c 7.5 %), van Dijk et al. determined that type 2 diabetes patients experience hyperglycemia...
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(glucose concentrations >180 mg/dl) 38 ± 4 % of the day. Moreover, the researchers found that even diabetes patients with an HbA1c <7 % experienced hyperglycemia for as much as 24 ± 5 % of the time throughout the day.

Using masked CGM to examine the correlations between HbA1c levels and metabolic control (average glucose) with various measures of glycemic variability in 68 patients (33 of whom had type 2 diabetes), Sartore et al. found no significant correlation between average glucose or HbA1c and the variability measures (e.g., SD). The authors concluded that HbA1c levels reflect averages and sustained hyperglycemic fluctuations, but are not sensitive to short and rapid glucose swings during a 24-hour period. They suggested that SD should be a fundamental parameter for optimal diabetes management.17

Duration of Glucose Excursions
Additionally, CGM and RT-CGM give information regarding the duration of glucose excursions contributing to glycemic variability. The identification of glucose trends and periods of hypoglycemia and hyperglycemia may induce more timely and more accurate intensification of therapy when indicated.

Disadvantages of Realtime Continuous Glucose Monitoring—The Provider’s Perspective
The effective use of RT-CGM requires that providers take time to review and understand the glucose graphs and trends in order to make the most appropriate treatment decisions. In the absence of a diabetes educator, providers who wish their patients to use RT-CGM may also need to instruct them in its use. Finally, a substantial amount of documentation regarding the need to use CGM or RT-CGM, especially in non-insulin-treated patients, will require time to complete, which may not be compensated by third-party payers.

Advantages of Realtime Continuous Glucose Monitoring—The Patient’s Perspective
Before discussing advantages of RT-CGM from the patient’s perspective, it is important to consider why SMBG is not as effective as it might be in patients with type 2 diabetes—especially those who are non-insulin-treated—and why its use is controversial.

Use of Self-monitoring of Blood Glucose
The findings from several reviews and meta-analyses suggest that SMBG is of limited clinical effectiveness in improving glycemic control in people with type 2 diabetes on oral agents or diet alone. Many of the studies suffered from methodological limitations and differed widely in the way self-monitoring results were used by providers and patients— if used at all. The systematic reviews and the RCTs that did report a reduction in HbA1c and did find favorable results included an educational component and/or feedback, with SMBG being used as a tool to change medication regimens or to inform patients.18,19

Unlike acute illness, diabetes requires patients to use several complex cognitive and physical tasks in order to actively manage their disease all day, every day. Successful SMBG involves effective problem-solving skills, an understanding about how to use the glucose data to make behavioral changes, clarity about the necessity of performing SMBG (since this is often not reviewed during appointments with providers), perception of the seriousness of the disease, perception of the benefit versus burden of treatment, and adequate professional and personal support.

Problem-solving has been identified as the most difficult skill not only for diabetes educators to teach, but also for diabetes patients to learn.20 According to Glasgow et al., diabetes patients report receiving inadequate amounts of support for problem-solving.21 Bohlen et al. examined whether patients with type 2 diabetes and their clinicians discussed burden of treatment during routine primary care visits.22 Forty-six primary care visits were videotaped and independently reviewed by two coders. Forty-three visits (93.5 %) contained burden of treatment discussions, 12 of them involving monitoring, 28 treatment administration, 19 access, and 24 treatment effects. The researchers concluded that burden of treatment discussions usually arise during visits, but rarely result in problem-solving efforts.

Many psychological and environmental factors are related to a lower frequency of SMBG use; they include lower levels of self-esteem, self-efficacy, and competence; higher levels of anxiety, depression, perceived painfulness of monitoring procedures, lifestyle interference, and inconvenience of SMBG; and, for adult patients, lack of family support.23 Fisher et al. determined that a substantial proportion of participants (type 1 and type 2 diabetes) scored as SMBG uninformed, unmotivated, and unskilled on specific assessment items, and that patients who were less informed, less motivated, and less behaviorally skilled reported lower frequency of SMBG.24

Use of Structured Self-monitoring of Blood Glucose
It is well established that post-prandial hyperglycemia significantly contributes to glycemic control in patients with type 2 diabetes, but few providers instruct their type 2 diabetes patients to check post-prandial glucose levels. That, together with the reasons described previously for SMBG ineffectiveness and poor adherence among type 2 diabetes patients, illustrates the fact that both providers and patients are attempting to establish glycemic control with, at best, incomplete information. Findings from recent studies, however, demonstrated that paired or structured SMBG (i.e., testing pre- and post-prandial blood glucose)—together with specific education addressing how to perform SMBG, how to modify diet and level of physical activity according to blood glucose, and what actions to take in case of abnormal values—can promote problem-solving skills, self-efficacy, and behavioral changes. Findings of studies using structured SMBG demonstrated that testing pre- and post-prandial blood glucose levels empowered patients to make healthy decisions about diet and physical activity and providers to make data-driven choices about which one of the numerous medications might be the most effective.25,26

Compared with usual care, structured testing resulted in significant improvements in HbA1c and significant reductions in PPGEs and overall glycemic variability.26,27

Although structured testing is a promising method of more clearly identifying the extent of glycemic variability and informing treatment decisions, neither long-term patient adherence nor sustained behavior change have been established. Siegelaar et al. suggested that much more frequent SMBG would be required to grasp the full extent of
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Glucose variability throughout a patient’s usual routine over several days. They further suggested that the psychological and financial burden for most diabetes patients may well exceed the benefit. The literature confirms that glycemic variability is not limited to type 1 diabetes or insulin-treated type 2 diabetes patients, but can occur for several hours/day even in well controlled type 2 diabetes patients (HbA1c <7.0 %). Given the emerging understanding of the impact of glycemic variability on the development and severity of long-term diabetes complications and the explosive prevalence of type 2 diabetes, it is essential to provide additional methods to assist those with type 2 diabetes achieve and maintain glycemic control.

Realtime Continuous Glucose Monitoring Provides Information Otherwise Not Available

People with diabetes face daily challenges when attempting to manage glucose levels and avoid hyperglycemic and/or hypoglycemic excursions. Both severe hypoglycemia and extreme hyperglycemia have an immediate and a long-term impact on cognitive and physical functioning. Even frequent SMBG does not enable many people with type 2 diabetes to adequately manage blood glucose levels, nor does it always capture marked and sustained hyperglycemic excursions. CGM and RT-CGM are increasingly used in children and adults with type 1 diabetes to maintain target HbA1c levels while limiting the risk of hypoglycemia. In adults with type 2 diabetes, the intermittent use of both CGM and RT-CGM has been shown to provide additional insights regarding glucose levels, time spent in target range, and time spent in hyperglycemia.21