The Changing Landscape of Glycemic Targets: Focus on Continuous Glucose Monitoring

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Continuous glucose monitoring (CGM) provides comprehensive assessment of daily glucose measurements for patients with diabetes and can reveal high and low blood glucose values that may occur even when a patient's A1C is adequately controlled. Among the measures captured by CGM, the percentage of time in the target glycemic range, or "time in range" (typically 70–180 mg/dL), has emerged as one of the strongest indicators of good glycemic control. This review examines the shift to using CGM to assess glycemic control and guide diabetes treatment decisions, with a focus on time in range as the key metric of glycemic control.

For individuals with diabetes, hyperglycemia and hypoglycemia present the greatest risks with regard to developing complications of diabetes, yet many patients are unaware of their daily blood glucose highs and lows. Traditionally, A1C has been the gold standard for assessing glycemic control, and A1C over time has shown a clear association with the development of vascular complications of diabetes (1–4). However, the use of continuous glucose monitoring (CGM) systems to measure interstitial glucose concentrations throughout the day has grown in recent years, supplanting multiple daily finger sticks for many patients and clinicians. This review summarizes the shift to using CGM to guide treatment decisions, with a focus on glycemic time in range (TIR) as the key indicator of glycemic control.

Limitations of A1C

A1C has long been the benchmark for assessing blood glucose control in patients with diabetes (5), although it is limited by an inability to monitor hypoglycemia. A1C can also be used to compare glycemic trends in a population over time or between populations (1). Because

A1C reflects average blood glucose concentrations over ~2–3 months, it does not address glycemic variability or hyperglycemic and hypoglycemic events. Patients with the same A1C may spend drastically different amounts of time in both high and low blood glucose ranges (Figure 1). Furthermore, for any single patient, the amount of time spent in high and low blood glucose ranges can vary greatly from day to day. Severe hypoglycemia could occur in patients with diabetes across varying A1C values (6). Therefore, perhaps the most important limitation of A1C is the lack of information it provides on hypoglycemic events (7). Without such information, the fear of hypoglycemia may limit some patients' adherence to treatment (8), thus negatively affecting glycemic control.

Another limitation of A1C is that differences in how red blood cells bind glucose can lead to variations in A1C across individuals and races. Conditions such as hemoglobinopathies, hemolytic anemia, chronic renal failure, and pregnancy, among others, affect red blood cell turnover, thereby altering the mean glucose-to-A1C relationship (9,10). The mean glucose-to-A1C relationship also is affected by race, with black individuals having an A1C ~0.4% (4.4 mmol/mol) higher than white individuals for a given mean glucose concentration (11). An analysis of the mean glucose-to-A1C relationship across three randomized studies using CGM in patients with type 1 or type 2 diabetes showed a wide range of glucose concentrations associated with a given A1C (1). These examples highlight the need for additional assessment of an individual's glycemic control using CGM.

Use of Continuous Glucose Monitoring

In recent years, CGM systems have undergone improvements in accuracy, reliability, safety features,

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FIGURE 1 A depiction showing how patients with the same A1C value may experience different amounts of TIR.

convenience, and reimbursement, leading to increasing numbers of patients incorporating CGM into their daily self-management (12). A range of personal CGM devices are available for patients with diabetes, and professional CGM systems owned by health care professionals are used periodically to monitor patients over time.

Current stand-alone CGM sensors marketed in the United States include four real-time CGM systems (Dexcom G5 sensor and G6 sensor [Dexcom, San Diego, CA], Eversense sensor [Senseonics, Germantown, MD], and Guardian Connect sensor [Medtronic, Minneapolis, MN]) and one intermittently scanned CGM system (FreeStyle Libre [Abbott Diabetes Care, Alameda, CA]). Personal CGM devices provide patients with feedback on current and impending glycemic status, allowing them to respond to glycemic events in real time, as discussed further below, and are particularly useful for patients with type 1 diabetes and insulin-requiring type 2 diabetes.

Periodic use of professional CGM devices can help manage all patients with diabetes. These devices include the Dexcom G4 Platinum Professional system (Dexcom, San Diego, CA), the FreeStyle Libre Pro system (Abbott Diabetes Care, Alameda, CA), and the Medtronic iPro2 (Medtronic, Minneapolis, MN). In addition, the Dexcom G6 Pro system (Dexcom, San Diego, CA) was approved by the U.S. Food and Drug Administration (FDA) in 2019 and is available to many clinics across the country, with full access anticipated by June 2020. Professional CGM systems include the option for blinded collection of glucose data when clinically necessary. “Blinded mode” allows health care providers to assess patients’ glucose patterns in real-world conditions in which their nutritional choices, exercise, behavior, and changes to medications are not influenced by self-adjusting in response to feedback from the CGM device. In “unblinded mode,” professional CGM devices can be used by patients intermittently as part of their daily self-management. Professional CGM offers patients a short-term option to

explore the benefits of CGM and can lead to a better understanding of factors that can influence glycemia, and retrospective review of the CGM data collected provides further input to clinicians for efficient management of patients’ treatment plan. These data allow clinicians to evaluate the effects of therapy in a timelier manner rather than waiting for A1C results several months after initiating or adjusting therapy.

CGM systems measure interstitial glucose concentrations every few minutes using a subcutaneous sensor and should be used for a minimum of 7 days and ideally for at least 14 days to gather enough data for interpretation (1,13,14). Because CGM provides comprehensive assessment of daily glucose, it can reveal the highs and lows in glucose concentrations that may occur even when a patient’s A1C is adequately controlled. While some time spent with glucose excursions outside of the target range is to be expected, individual average CGM tracings have revealed substantial between-patient variability among patients with type 2 diabetes who were being treated with oral glucose-lowering therapy and had identical A1Cs of 6.5% (15). Most patients had glucose excursions above the target glycemic range despite achieving their A1C goal.

Personal CGM allows patients to respond to acute glycemic events in real time and adjust insulin doses, food selections, and activity accordingly. CGM systems include trend arrow information, which helps patients respond to anticipated high or low blood glucose concentrations and by proactively adjusting medication to prevent hyperglycemia or hypoglycemia. As guidance, Aleppo et al. (16) and Kudva et al. (17) published practical recommendations for using trend arrows to adjust insulin doses for the Dexcom G5 CGM system and the FreeStyle Libre Flash CGM systems, respectively. In addition, customizable alarms and alerts are available on real-time CGM systems to automatically warn patients of current or impending high or low blood glucose concentrations (12).

CGM system reports show blood glucose measures in a number of ways, including the ambulatory glucose profile (AGP) and blood glucose statistics, providing clinicians and patients with a variety of measures to evaluate glycemic control (Figure 2) (12). The AGP is based on glucose concentration data collected and averaged over multiple days to visualize the 24-hour glucose concentration tracing. Key CGM metrics over a 24-hour period are also reported, including mean glucose, time in hypoglycemia, TIR, and time in hyperglycemia. In addition, CGM reports display some measures of glycemic variability (e.g., coefficient of variation, glucose SD, and mean

FIGURE 2 Electronic CGM reports allow for visualization of AGP and key glucose metrics. Reproduced with permission from Kruger et al. Diabetes Educ 2019;45(Suppl. 1):3S–20S [ref. 12].

amplitude of glycemic excursion [MAGE]; Supplementary Table S1) (18–20). Although its importance is still under investigation, glycemic variability has been linked to complications of diabetes, and studies have shown improvements in glycemic variability with different classes of glucose-lowering therapy, as will be further discussed.

The above measures allow both clinicians and patients a better assessment of an individual's level of glycemic control. Because patients have a better understanding of A1C and are accustomed to using A1C as a key indicator of glycemic control, it is important to explain to patients the various measures captured with CGM. A step-by-step process for reviewing AGPs and blood glucose statistics with patients is shown in Table 1 (12).

CGM allows for more comprehensive assessment of hypoglycemia, including unrecognized or asymptomatic hypoglycemia, because the device records glucose concentrations throughout the day, including during times that would be missed with self-monitoring of blood glucose (SMBG) using finger sticks (e.g., during sleep or exercise). A study of patients with type 2 diabetes revealed that the majority of patients who demonstrated hypoglycemia by CGM were unaware of their hypoglycemia (21). This finding is consistent with the all-too-common complication of hypoglycemia unawareness (22,23).

To limit this danger, hypoglycemia should always be addressed first during CGM interpretation, and a discussion of hypoglycemia symptoms should be initiated

TABLE 1 CGM Data Interpretation Using the AGP

Step 1	Confirm that adequate data are available. For current CGM users, a minimum of 70% of 2 weeks of data is recommended. Fewer days are needed when professional CGM systems are used.
Step 2	Print out the AGP and ask patients to describe their daily self-management. When are they taking their insulin and how much? When do they wake? When do they eat? Do they exercise, and, if so, what type of exercise and when are they doing it? Do they drink alcohol, and, if so, is it daily? Document this information on the AGP printout.
Step 3	Ask patients what they see in the AGP and why they think it may be important. Then listen. Interactive discussion with patients allows them to better understand how their insulin, food, and other factors affect their glucose levels and also helps clinicians identify knowledge deficits or behaviors that may not support glycemic goals.
Step 4	Look for problematic glycemic patterns in the following order of priority: 1. Hypoglycemia 2. Hyperglycemia 3. Wide glycemic variability Review the overall glucose profile (initial view) to determine the time of day when patterns are occurring, and then review the daily graphs to double-check patterns to see if they are clustered on certain days.
Step 5	Encourage patients to reflect on what they think may be causing the problem and discuss potential solutions.
Step 6	Collaboratively develop an action plan. Make sure patients fully understand the changes they will be making and that they have the knowledge and skills to implement the plan.
Step 7	Make a copy of the marked-up AGP printout for the patient and enter the original into the EMR. If electronic entry is not possible, copy and paste the AGP into the EMR as a progress note.

Adapted from Kruger et al. (12). EMR, electronic medical record.

with all patients. Asymptomatic hypoglycemia among patients with type 2 diabetes has also been associated with low mean glucose values and a high SD around the mean glucose value (24). The availability of customizable alarms to alert patients of impending low blood glucose is an important feature of real-time CGM systems, especially for patients experiencing nocturnal hypoglycemia, frequent severe hypoglycemia, impaired hypoglycemia awareness, or fear of hypoglycemia (12).

On the other hand, although CGM systems have improved in accuracy, a short lag between SMBG readings and CGM readings of interstitial glucose can still exist. A study in patients with type 1 diabetes found that a drop in glycemia during prolonged aerobic exercise lagged by a mean of 12

minutes when measured by CGM versus SMBG, with a mean absolute relative difference for CGM versus SMBG of 13% (25). Therefore, patients should be advised to be vigilant during exercise and confirm any suspected hypoglycemia with a fingerstick glucose measurement.

CGM also provides patients with diabetes with a better assessment of pre- and postmeal glucose concentrations compared with SMBG (26), and this improved assessment helps inform patient behavior and medication adjustments. Multiple clinical studies have demonstrated benefits of CGM compared with SMBG, including consistent improvements in glycemic control and less hypoglycemia in patients with type 1 (27–30) or type 2 (31–35) diabetes. For example, the DIAMOND (Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes) study, which included patients with type 1 or type 2 diabetes on multiple daily insulin injections, reported significantly greater improvements in A1C after 24 weeks with CGM versus usual care with SMBG (type 1 diabetes: -1.0 vs. -0.4% [-11.0 vs. -4.3 mmol/mol]; type 2 diabetes: -0.8 vs. -0.5% [-8.7 vs. -5.5 mmol/mol]) (27,35). Patients with type 1 diabetes in the CGM group spent less time with blood glucose <70 mg/dL compared with those in the SMBG group (median of 43 vs. 80 minutes/day), whereas interpretation of the effect of CGM on hypoglycemia in patients with type 2 diabetes was limited by an extremely low amount of time with blood glucose <70 mg/dL at baseline. Likewise, a study of various treatment regimens, including diet and exercise, oral glucose-lowering medications, exenatide, and/or basal insulin, demonstrated a significant improvement in A1C after 12 weeks with intermittent CGM versus SMBG (-1.0 vs. -0.5% [-11.0 vs. -5.5 mmol/mol]), which was sustained over 1 year of follow-up (33). This result was not associated with more hypoglycemia.

The benefits of using CGM as part of a diabetes management plan have been recognized by clinical associations in recent years, with guidelines from the American Diabetes Association (ADA), the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE), the Endocrine Society, and an international consensus from the Advanced Technologies & Treatments for Diabetes (ATTD) Congress recommending the use of CGM in patients with type 1 diabetes and some patients with type 2 diabetes, especially those receiving intensive insulin therapy or having a history of hypoglycemia or high glycemic variability (Table 2) (5,18,36–38). In addition, the ATTD Congress recently updated its guidance to provide recommended targets for CGM-derived time in glucose ranges (39).

TABLE 2 Guideline Recommendations for the Use of CGM in Patients With Type 2 Diabetes

Organization	Recommendation
AACE/ACE (37)	Consider the use of professional CGM (i.e., the clinician's device) in patients with type 2 diabetes who have not reached their glycemic target within 3 months of initial glucose-lowering therapy and for those whose therapy is associated with a risk of hypoglycemia. Consider the use of personal CGM devices in patients with type 2 diabetes who are receiving intensive insulin therapy, those with a history of hypoglycemia unawareness, or those with recurrent hypoglycemia.
ADA (36)	In patients prone to glycemic variability, such as those with type 2 diabetes with severe insulin deficiency, glycemic control is best assessed using a combination of A1C and measures of daily glucose such as SMBG or CGM.
Endocrine Society (38)	Short-term, intermittent use of real-time CGM is suggested for adult patients with type 2 diabetes (not on prandial insulin) who have an A1C $\geq 7\%$ and are willing and able to use the device.
ATTD international consensus (18)	CGM should be considered in conjunction with A1C for glycemic status assessment and therapy adjustment in patients with type 2 diabetes treated with intensive insulin therapy who are not achieving glucose targets, especially if the patient is experiencing problematic hypoglycemia.

Vascular Complications Linked to Glucose Variability

Just as A1C has shown a clear association with microvascular and macrovascular complications of diabetes, glucose variability measures derived from CGM have also been linked to long-term complications. For example, MAGE has been associated with oxidative stress, which potentially contributes to microvascular and macrovascular complications (40). Higher MAGE and more severe hypoglycemic episodes were also associated with an increased incidence of ventricular extrasystoles among patients with type 2 diabetes and cardiovascular disease (CVD) who were using insulin and/or sulfonylurea treatment (41). Even among individuals without prevalent CVD or previously diagnosed diabetes, high glucose concentrations in the 2-hour oral glucose challenge were associated with the risk of cardiovascular events independent of other measures of hyperglycemia (42). These data suggest that high glycemic variability may be associated with vascular complications of diabetes, supporting the use of CGM to evaluate treatment responses and help guide diabetes management decisions.

Time in Range

Among all of the glycemic measures captured by CGM, TIR has emerged as one of the strongest indicators of good glycemic control. It should be noted that, for patients without access to CGM, TIR can be estimated using 7-point SMBG profiles (fasting, 2 hours after breakfast, before lunch, 2 hours after lunch, before dinner, 2 hours after dinner, and bedtime) once weekly. Alternative testing with 1,5-anhydroglucitol has been used as a surrogate marker for postprandial glucose excursions and short-term hyperglycemia but has limitations (43), and

insurance coverage may not make this option more affordable than CGM.

The daily percentage of TIR is increasingly being used as the key metric to assess glycemic control (Figure 3). Although different target ranges have been proposed (e.g., 70–140 mg/dL), a range of 70–180 mg/dL has become widely accepted. However, clinicians and patients can choose different ranges based on each patient's ultimate goal. TIR goals must be customized for individual patients with the aim of achieving the greatest TIR without increasing hypoglycemia. In February 2019, the ATTD Congress convened a panel of individuals with CGM expertise, including clinicians, researchers, and patients with diabetes, to develop clinical CGM targets for TIR (39). For patients with type 1 diabetes or type 2 diabetes, a TIR of $>70\%$ was proposed as a reasonable goal, and a time below range of $<4\%$ was recommended. For patients at higher risk of hypoglycemia because of older age, duration of diabetes, duration of insulin therapy, greater prevalence of hypoglycemia unawareness, or comorbidities, TIR of $>50\%$ and time below range $<1\%$ were recommended.

Time out of range has been recognized as an important measure linking glycemia with diabetes complications. Among patients with type 1 or type 2 diabetes, the more time is spent in range, the lower rates of microvascular complications such as retinopathy and microalbuminuria will be (44,45).

Because A1C is widely recognized as the standard measure of glycemic control, clinicians have sought to interpret the association between TIR and A1C. TIR (measured over at least 10 days at baseline and at least 14 days at 6 months) showed a moderate correlation with A1C in an analysis of four randomized trials that included

FIGURE 3 TIR defined. Reference ranges help clinicians guide therapy recommendations.

545 adults with type 1 diabetes, although it was still associated with a wide range of A1C values (46). For example, a mean TIR of 50% was associated with an A1C of $\sim 8.0\%$ (64 mmol/mol), with a range of 6.6–9.2% (49–77 mmol/mol). Change from baseline to 6 months for TIR was loosely correlated with a wide range of A1C changes. On average, an increase in TIR of 10% roughly corresponded to a decrease in A1C of $\sim 0.6\%$ (6.6 mmol/mol).

At the urging of the FDA, a new metric for correlating CGM data with well-established A1C data were developed: the glucose management indicator (GMI) (47). In clinical practice, GMI based on the past 2 weeks of CGM data can be used to estimate a patient's A1C over time.

Treatments Evaluated by CGM

Glucose-lowering therapies have traditionally been evaluated based on their effect on glucose concentrations over long periods of time (e.g., A1C) or at specific time points (e.g., fasting plasma glucose and postprandial glucose). The advancement of CGM technology and the emphasis on maximizing TIR have heightened interest in using CGM to evaluate treatments.

Pramlintide is an analog of the β -cell hormone amylin that reduces postprandial hyperglycemia through suppression of inappropriate postprandial glucagon secretion, slowing of gastric emptying, and increasing satiety leading to caloric reduction and weight loss (48,49). It was one of the first drugs for which CGM was used to demonstrate the benefits of increasing TIR, with less time in hyperglycemia and no increase in hypoglycemia, among patients with type 1 diabetes (50).

Glucagon-like peptide-1 (GLP-1) receptor agonists stimulate insulin secretion and suppress glucagon

secretion, both in a glucose-dependent manner, and are thus associated with a lower risk of hypoglycemia compared directly to insulin and sulfonylureas (51). GLP-1 receptor agonists also slow gastric emptying and reduce appetite, which contribute to lowering postprandial glucose (52). In a 10-week study using CGM to evaluate treatment, exenatide once weekly added to metformin increased TIR to 77% of the day, compared with 58% of the day for placebo, with no increase in time spent in the hypoglycemic range (Figure 4), along with reductions in daily mean glucose, the daily glucose profile, MAGE, and glucose SD (53). The short-acting GLP-1 receptor agonist exenatide twice daily added to insulin glargine also increased TIR to 76% in a 26-week clinical study (54) and to 63% in a 32-week clinical study that used a more stringent definition of TIR (70–140 mg/dL) (55). Similar improvements in TIR were seen with dulaglutide when used with rapid-acting insulin (56).

Sodium–glucose cotransporter 2 (SGLT2) inhibitors increase glucose elimination via the kidneys and reduce hyperglycemia through insulin-independent mechanisms. A 4-week study showed that the SGLT2 inhibitor dapagliflozin increased TIR to 70% and reduced mean blood glucose, MAGE, and glucose SD among patients with type 2 diabetes (19). Likewise, improvements in TIR were observed among patients with type 1 diabetes treated with SGLT2 inhibitors (dapagliflozin, empagliflozin, or canagliflozin) or the SGLT1/2 inhibitor sotagliflozin (57–63).

Conclusion

Patients and clinicians have become increasingly aware of the utility of CGM for comprehensive evaluation of blood glucose concentrations. CGM is useful for patients with type 1 diabetes and certain patients with type 2 diabetes, particularly those treated with intensive insulin therapy or having a history of hypoglycemia or high glycemic variability. Personal CGM should be considered for patients with type 1 diabetes and those with type 2 diabetes requiring insulin, as well as those who want to learn more about how their lifestyle affects their glucose in real time without a finger stick. Professional CGM can help manage all patients with diabetes periodically over time; it also allows clinicians to evaluate therapy in real time rather than waiting for A1C results.

Although A1C undoubtedly remains an important measure of glycemic control, treating to the A1C goal alone without considering the daily peaks and troughs in glucose concentrations increases the risk that patients may still be experiencing frequent and/or dangerous

FIGURE 4 Mean proportions of time spent in glycemic ranges after treatment with exenatide once weekly or placebo, each added to metformin. * $P < 0.001$, treatment difference [exenatide once weekly – placebo] in least-squares mean changes. MET, metformin. Reproduced with permission from Frías et al. [53].

out-of-range glucose concentrations. TIR has emerged as perhaps the most important glycemic target linking improvements in glucose control with better patient outcomes. In clinical trials using CGM, newer classes of glucose-lowering therapies have been found to be associated with increased TIR and improved measures of glycemic variability. Thus, we propose that clinicians rely heavily on TIR data derived from CGM where possible for diabetes management decisions.

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AUTHOR CONTRIBUTIONS

P.R.K. and D.F.K. each contributed to the conception of the article and critically revised the manuscript for important intellectual content. P.R.K. is the guarantor of this work and, as such, takes responsibility for its integrity.

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