The Utility and Interpretation of Ambulatory Glucose Profiles

Introduction
Achieving the glycemic target—a key goal of diabetes management—remains elusive despite pharmacological and technological advances in insulin delivery and glucose monitoring. Monitoring glycated hemoglobin A1c (HbA1c) remains the standard of care for assessing diabetes control, as it has been correlated with micro- and macrovascular complications. However, since the HbA1c reflects the mean blood glucose over 8 to 12 weeks, it does not provide insight regarding day-to-day diabetes control, the impact of hypo- or hyperglycemia, or the magnitude of glucose variability. Self-monitored blood glucose (SMBG) via fingersticks is used to guide day-to-day adjustment of therapy with the goal of improving overall glycemic control as measured by HbA1c. A limitation of SMBG is that it yields glucose level information for only specific moments in time. As such, significant hypo- and hyperglycemic events are often missed. The episodic and patient-dependent nature of SMBG also makes overnight data impractical to obtain, and is subject to underreporting and difficulty interpreting the results of patient-maintained logbooks.

The shortcomings in these approaches led to a role for continuous glucose monitoring (CGM), which provides blood glucose levels throughout the day and night to assist with clinical decision-making. There can be barriers to widespread effective use of CGM in clinical practice, including start-up costs and lack of reimbursement, provider knowledge of how to use the data, and a daunting time investment required of providers to become proficient at interpreting the variety of output reports available from various CGM devices.

The ambulatory glucose profile (AGP) addresses the challenge with data analysis by providing standardized, easily understandable, and actionable output from the various commercially available CGM devices. In this regard, AGP has been likened to an electrocardiogram (ECG) for glucose patterns—differ-
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THE UTILITY AND INTERPRETATION OF AMBULATORY GLUCOSE PROFILES

ent devices (in this case CGMs instead of ECG machines) providing the same standardized output to guide assessment and treatment.1

This article discusses CGM and the role of AGP in aggregating CGM data into actionable information to inform decisions regarding diabetes management.

CGM Technology
CGM consists of a subcutaneous sensor which measures the glucose level in interstitial fluid and transmits data to a receiver, smartphone, or directly to an insulin pump.6 Unlike SMBG fingersticks which provide only “snapshots”, CGM provides blood glucose level data every 5 minutes (288 times per day) to allow tracking of blood glucose trends (ie, the direction and rate of glucose change).

A limitation of CGM is that there may be a natural physiologic delay associated with the transfer of glucose from the blood vessels into the interstitial compartment of the body which is accentuated when glucose levels are undergoing rapid change. This largely accounts for the 5- to 15-minute delay between CGM readings and blood glucose meter readings.7 Nevertheless, CGM and blood glucose fingerstick measurements correlate closely and their trends (direction and speed or rate) of glucose change are similar. Despite this limitation with CGM, its use has been shown to improve glycemic control by means of lowering HbA1C without significantly increasing the frequency or severity of hypoglycemic episodes.5,14

CGM devices are currently approved only as adjunctive use to complement SMBG, requiring a confirmatory fingerstick before making any treatment decisions.7 In July 2016, an FDA advisory panel recommended approval of the Dexcom G5 Mobile CGM system for non-adjunctive use, meaning that a confirmatory fingerstick would no longer be required to make treatment decisions.8 The panel’s recommendation was based, in part, on improved accuracy and reliability of the Dexcom G5 Mobile CGM system. With the G5 system, a mean absolute relative difference (MARD) (ie, % error) <10% compared to YSI reference standards has been shown.8 In comparison, other CGM systems have shown a MARD of approximately 10% to 11% or less compared with SMBG,5,9,10 with clinically important differences in accuracy and performance among the CGM systems.11,12

The proposed change with the Dexcom G5 Mobile CGM system would allow patients to use CGM-based treatment decisions, specifically the CGM number and rate of change arrows, when considering
any treatment decision without first confirming with a
fingerstick from a blood glucose meter. Additionally,
the Dexcom G5 CGM system provides contextual in-
formation that SMBG meters do not provide that may
lead to users making more informed insulin dosing
decisions and proactive treatment decisions, which
in turn may allow for better glucose management and
outcomes.\(^\text{13}\) The FDA had not approved the new indi-
cation at the time this article was finalized.

The REPLACE-BG study (N=225) is currently
underway to determine whether the routine use of
CGM without SMBG confirmation is as safe and ef-
effective as CGM used as an adjunct to blood glucose
monitoring in patients with type 1 diabetes.\(^\text{14}\)

Insulin-treated patients are prone to impaired
awareness of hypoglycemia, and hypoglycemia im-
pairs physiological and behavioral defenses against
subsequent falling blood glucose levels, resulting in
a cycle of recurrent hypoglycemia.\(^\text{15}\) Patients with
type 2 diabetes also may lose awareness of hypogly-
cemia over time, especially if treated with insulin or
disulfonylureas.\(^\text{15,16}\) It is estimated that hypoglycemia
is the cause of death in 2% to 10% of people with type 1
diabetes; moreover the cost of admission for a hypo-
glycemic episode is over $17,000.\(^\text{15,17}\)

**CGM Benefits**

Trials specifically designed to reduce hypoglyce-
mia in patients with a high risk have demonstrated
a reduction in hypoglycemia with CGM.\(^\text{18,19}\) There is

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**TABLE 1  Comparison of professional and personal continuous glucose monitoring**\(^7\)

<table>
<thead>
<tr>
<th>Professional CGM</th>
<th>Personal CGM</th>
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<tbody>
<tr>
<td><strong>Benefits</strong></td>
<td></td>
</tr>
<tr>
<td>• Provides insight into trending information/pattern management</td>
<td>• Early warning of high and low glucose levels and/or rapidly changing glucose allows for early intervention</td>
</tr>
<tr>
<td>• Identifies insulin action (insulin dose effect) and potential need for additional adjustments/medications to control post-prandial glucose</td>
<td>• Provides a means to identify glycemic patterns, enabling more appropriate medication adjustments</td>
</tr>
<tr>
<td>• Provides information about timing of food digestion and timing of insulin administration</td>
<td>• Helps patients with reduced hypoglycemia awareness avoid hypoglycemic episodes</td>
</tr>
<tr>
<td>• Provides continuous data for overnight basal testing and assessment of nocturnal hypoglycemia</td>
<td>• Directional arrows to indicate direction of blood glucose level</td>
</tr>
<tr>
<td>• Finds patterns that otherwise could not be detected by finger stick alone</td>
<td>• Particularly helpful in guiding adjustments to address glycemic patterns during nonroutine activities, such as exercise or stressful situations</td>
</tr>
<tr>
<td>• Finds patterns of undetected low blood glucose in patients at treatment goal</td>
<td>• Allows for attainment of improved glycemic control within a short period of time</td>
</tr>
<tr>
<td>• Allows efficient and effective identification of areas of clinical challenge and application of appropriate medical management to address that specific clinical issue</td>
<td>• Provides superior data to fingerstick monitoring in regards to frequency and consistency</td>
</tr>
<tr>
<td>• Early warning of high and low glucose levels allows for early intervention</td>
<td>• Allows for more aggressive, individualized insulin titration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Candidates</th>
<th></th>
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<tbody>
<tr>
<td>• Those that fear hypoglycemia, but are consistently hyperglycemic, provides visual feedback to allay fear</td>
<td>• Those that fear hypoglycemia, but are consistently hyperglycemic, provides visual feedback to allay fear</td>
</tr>
<tr>
<td>• Uncontrolled type 1 or type 2 diabetes</td>
<td>• Uncontrolled type 1 or type 2 diabetes</td>
</tr>
<tr>
<td>• Hypoglycemia unawareness</td>
<td>• Hypoglycemia unawareness</td>
</tr>
<tr>
<td>• Pregnancy or wants to become pregnant*</td>
<td>• Pregnancy or wants to become pregnant</td>
</tr>
<tr>
<td>• Individuals who have hemoglobin A1c at or below treatment goal and state they have no hypoglycemia</td>
<td>• Individuals who have hemoglobin A1c at or below treatment goal and state they have no hypoglycemia</td>
</tr>
<tr>
<td>• Children</td>
<td>• Children</td>
</tr>
<tr>
<td>• Patient that needs to be convinced to intensify therapy</td>
<td>• Patient that needs to be convinced to intensify therapy</td>
</tr>
<tr>
<td>• Not at treatment goals but trying very hard to get there</td>
<td>• Not at treatment goals but trying very hard to get there</td>
</tr>
<tr>
<td>• Gastroparesis</td>
<td>• Gastroparesis</td>
</tr>
<tr>
<td>• Needs/wants to make lifestyle change</td>
<td>• Needs/wants to make lifestyle change</td>
</tr>
<tr>
<td>• New to practice: trying to determine where the patient has been to help develop a management plan moving forward</td>
<td>• Interested in an insulin pump or wishes to own CGM</td>
</tr>
</tbody>
</table>

*No professional CGM is currently approved by FDA for use in pregnancy.
Abbreviation: CGM, continuous glucose monitoring.
also some evidence that CGM reduces patient fear of hypoglycemia, which is a significant barrier to good glycemic control.20

The use of CGM appears to have another benefit. Growing evidence indicates that significant glycemic variability—fluctuations in blood glucose levels particularly when accompanied by hypoglycemia, can contribute to the onset and progression of macro- and microvascular complications.12,21 Pathophysiologic data indicate that fluctuating glucose levels cause oxidative stress, and epidemiologic studies suggest a correlation between elevated postmeal glucose levels and adverse micro- and macrovascular outcomes.21,22 Furthermore, there is a significant association between
glycemic variability and an increased incidence of hypoglycemia, the latter of which induces increased platelet and neutrophil activation, and may trigger inflammation by inducing the release of inflammatory cytokines.21 Taken together, these observations suggest that glycemic variability, which is effectively assessed by CGM, is emerging as an additional target parameter for optimum glycemic control.4,21

Professional vs Personal CGM
CGM devices can be divided into 2 categories: professional and personal. Professional CGM is owned by the health care professional/institution and is typically worn by the patient for up to 7 days, then returned to the office for interpretation. By keeping a food and activity logbook while wearing the device, professional CGM assists in clinical decision-making and serves as a teaching tool for the patient to better understand the rationale for treatment changes. Professional monitoring can be done blinded (retrospective), with patients remaining unaware of monitoring results until they are downloaded and analyzed, or unblinded (real time), in which the patient is part of the decision-making.7

Personal CGM devices are owned by patients and their use is typically preceded by a trial with a professional CGM. Because the glucose data are not hidden, immediate therapeutic adjustments can be made by the patient in “real-time”.7 In addition, this enables the patient to see the effects on blood glucose of glucose-lowering medications, food, and activity, thereby facilitating behavior modification. A personal CGM device can be used with or without an insulin pump. Table 1 (see page S3) compares the benefits of and candidates for professional and personal CGM.7

Preliminary evidence indicates that use of CGM is very effective in lowering HbA1c and reducing the incidence of hypoglycemia in patients with type 1 diabetes mellitus treated with basal-bolus therapy.23 This finding suggests that CGM may play a broader role in the treatment of patients with T1DM. Similar investigation in patients with type 2 diabetes mellitus is ongoing.

While most insurance carriers reimburse for

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**Table 1**

<table>
<thead>
<tr>
<th>Professional CGM</th>
<th>Personal CGM</th>
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<tbody>
<tr>
<td>Owned by healthcare professional/institution</td>
<td>Owned by patients</td>
</tr>
<tr>
<td>Typically worn by the patient for up to 7 days</td>
<td>Worn by the patient</td>
</tr>
<tr>
<td>Assists in clinical decision-making</td>
<td>Enables immediate therapeutic adjustments</td>
</tr>
<tr>
<td>Can be done blinded or unblinded</td>
<td>Can be done only unblinded</td>
</tr>
</tbody>
</table>

**Abbreviations:** AGP, ambulatory glucose profile; IQR, interquartile range.

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**Figure 2**

Identifying glycemic trouble spots with the AGP

**Figure 2a.** AGP indicates periods of hypoglycemia from 4am to 8am and at 10pm; frequent hyperglycemia during the day between approximately 12 noon and 6pm.

**Figure 2b.** Blood glucose levels in target zone most of the day; hyperglycemic episodes around bedtime (12am to 2am) with no nocturnal hypoglycemia. Therefore, it would be reasonable to consider adjusting medication at bedtime to address the hyperglycemic episodes if needed.

**Figure 2c.** Median curve indicates frequent hyperglycemia between 6pm and 8pm; width of IQR curve (blue) and the 10th-90th percentile curve (outlined by broken lines) during that time period indicate significant glycemic variability as well, with blood glucose levels ranging from approximately 50 mg/dL to almost 300 mg/dL. Therefore, there is a potential risk for hypoglycemia if insulin dose is increased.

Abbreviations: AGP, ambulatory glucose profile; IQR, interquartile range.
The utility and interpretation of ambulatory glucose profiles

Figure 3. Case study

Figure 3a-d. Professional CGM output reports for this patient.

Figure 3e. Same data summarized in an AGP. AGP illustrates that while the patient is concerned about hypoglycemia, less than 1% of readings are in the hypoglycemic range. There is significant hyperglycemia between 8am and 8pm with much glycemic variability.

<table>
<thead>
<tr>
<th></th>
<th>27 Mar–02 Apr 15</th>
<th>03 Apr–09 Apr 15</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>0.0%</td>
<td>0.0%</td>
<td>N/A</td>
</tr>
<tr>
<td>Mean Glucose</td>
<td>162</td>
<td>187</td>
<td>15%</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>71</td>
<td>78</td>
<td>10%</td>
</tr>
<tr>
<td>% in Hypoglycemia (&lt;55 mg/dL)</td>
<td>3</td>
<td>2</td>
<td>-33%</td>
</tr>
<tr>
<td>% in Low (≥55 and &lt;80 mg/dL)</td>
<td>6</td>
<td>6</td>
<td>0%</td>
</tr>
<tr>
<td>% in Target (≥80 and ≤130 mg/dL)</td>
<td>29</td>
<td>16</td>
<td>-45%</td>
</tr>
<tr>
<td>% in High (≥130 and ≤240 mg/dL)</td>
<td>48</td>
<td>46</td>
<td>-4%</td>
</tr>
<tr>
<td>% in Hyperglycemia (&gt;240 mg/dL)</td>
<td>14</td>
<td>29</td>
<td>107%</td>
</tr>
<tr>
<td>Days Sensor Used</td>
<td>7</td>
<td>7</td>
<td>0%</td>
</tr>
</tbody>
</table>

Abbreviations: AGP, ambulatory glucose profile; CGM, continuous glucose monitoring.
professional CGM 2 to 4 times per year and interpretation for personal CGM 2 to 4 times a year. Medicaid and Medicare cover only professional CGM.24-26 The costs of the CGM equipment and interpretation of data are considerable but must be considered in the context of the costs to society for failure to implement CGM. These costs include costs associated with emergency management of hypoglycemia, impaired quality of life, reduced productivity, and long-term complications resulting from failure to achieve the optimal level of glycemic control.5

By way of comparison, ultrasounds and biopsies require significant upfront costs and are associated with procedural risks. Yet, these costs are more readily accepted because they provide vital information to guide critical clinical decision-making. CGM is associated with far fewer start-up costs, provides comparable reimbursement (in the case of thyroid ultrasound and biopsy, for example), is less time-consuming and associated with less risk, and provides vital clinical information to care for patients with diabetes.

Beyond cost, a key barrier to widespread utilization of CGM is the significant time investment required of the provider to become proficient managing and interpreting the large amount of data generated and the wide array of reporting options available.6 This barrier has led to the development of a standardized, easily understood, actionable analysis of CGM data.

Ambulatory Glucose Profile

The ambulatory glucose profile (AGP), developed by Mazze et al in collaboration with the International Diabetes Center in Minneapolis, Minnesota, is a nonproprietary, open-source universal software report that is intended to simplify clinical decision-making by providing an effective way to display glucose blood level data.1,27 The AGP data analysis program can utilize data from most CGM devices (except Medtronic), as well as SMBG monitor downloads. CGM data over several days—ideally 14 days—can be aggregated to statistically and visually characterize glycemic exposure, variability, stability, and time in target range (TIR). As a result, the AGP provides a comprehensive view of the patient’s changing glucose levels over time in an intuitive manner that allows clinicians and patients to make informed adjustments in treatment.1

Ambulatory glucose profile dashboard

The AGP ‘dashboard,’ or standard one-page report, consists of 3 parts (Figure 1, page S4):

- Statistical summary: includes glucose exposure (mean glucose and estimated HbA1C based on collected data), variability (standard deviation [SD] and interquartile range [IQR]), percentage of values in target range, or above or below target range (dangerously low, very low, low, high, very high, dangerously high), and data sufficiency (average number of tests per day upon which the data were generated).
- Visual display of typical glucose profile: a modal (standard or average) day derived by collapsing and plotting according to time (without regard to date) all data collected over multiple days (14 days is ideal, minimum is 7) as if they occurred over 24 hours. A smoothing algorithm is applied to data to generate 5 glucose curves (Figure 1, page S4): median (orange line), 25th & 75th percentile (solid blue lines), and 10th and 90th percentiles (dotted lines). The gray bar represents the target glucose range for the individual patient.
- Daily view: thumbnail view of the glucose profile (target range and median line) from each 24-hour period in a calendar format to facilitate discernment between work vs nonworkday and weekend vs weekday. Presenting the data in this way is intended to facilitate conversations with patients to identify circumstances that might be contributing to glucose variability or excursions.

In the visual display of the AGP (Figure 1, page S4), the median curve (orange line) is a representation of glucose stability, and the 25th to 75th percentile curve (bordered by the solid blue lines) contains 50% of the data and defines the IQR, representing glucose variability. The wider the curve, the more variable the glucose level during that time period. The 10th to 90th percentile curve (bordered by the dotted lines) tracks glucose excursions, representing outlier data and containing 80% of all the data. If the reason for excursions is unclear, data from individual days (daily view) may provide insight. The visual display facilitates identification of the times of day when glucose is consistently high or low, when the greatest variability occurs, and the magnitude of that variability. For example, the 10th percentile curve crossing 70 mg/dL or lower indicates a moderate risk of hypoglycemia at that time since consistently 10% of the values fall in this range. However, if the 25th percentile curve crosses into the hypoglycemic range, this implies a marked risk since it indicates that more than 25% of the glucose values fall within the hypoglycemic range. Consequently, this situation should be resolved before modifying treatment to address hyperglycemia.1

Use of the AGP to interpret CGM data aids blood
glucose management at both a ‘macro’ level, by identifying glycemic trouble spots to guide dosing adjustments (Figure 2, page S8), and at a ‘micro’ level by facilitating improved understanding of the interaction between food, physical activity, and medications that can improve patient insights and real-time diabetes decision-making.1

Case study
DB is a 54 year-old female with diabetes for the last 18 years. She monitors her blood glucose 2 to 4 times per day with whatever blood glucose monitoring device she has strips (eg, One Touch, Free Style, Aviva). Her HbA1c has ranged from 9.5% to 10.2% over the past several months. During that time, she has been managed with glargine and insulin aspart. She is fearful of hypoglycemia, which negatively impacts treatment adherence, resulting in persistent hyperglycemia. Figure 3a-d represents professional CGM output reports for this patient, and Figure 3e (see page S6) represents the same data summarized in an AGP. The AGP illustrates that while the patient is concerned about hypoglycemia, only 0.9% of her blood glucose readings are in the hypoglycemic range. Her daytime levels are generally within the target range, but there is significant hyperglycemia between 8pm and 8am with much glycemic variability. The information provided by the AGP enables modification of her treatment plan to specifically address the late evening and nocturnal hypoglycemia.

Summary
Continuous glucose monitoring is useful in a wide variety of patients with type 1 or type 2 diabetes for monitoring trends in the direction and rate of change in blood glucose levels. CGM is superior to fingerstick monitoring for improving glycemic control and reducing hypoglycemia. However, the large amount of data generated by CGM and lack of output standardization among available CGM devices contribute to barriers to widespread effective use of this valuable tool. The AGP provides an effective way to consolidate and display seven to 14 days of blood glucose data to help the clinician visualize the data as if they were viewing 24 hours of data. Thus, the AGP provides greater insight into several indicators of glycemic control, thereby enabling targeted clinical decision-making.

References