

deviation). As more fully explained in the article below, with the AGP in front of them, patients and clinicians can agree on a personalized treatment plan aimed at improving the glucose profile while avoiding significant hypoglycemia.

REFERENCES

1. Rubinow KB, Hirsch IB. Reexamining metrics for glucose control. *JAMA* 2011;305:1132–1133
2. Cryer PE. Glycemic goals in diabetes: trade-off between glycemic control and iatrogenic hypoglycemia. *Diabetes* 2014;63:2188–2195
3. Bergenstal RM, Gal RL, Connor CG, et al.; T1D Exchange Racial Differences Study Group. Racial differences in the relationship of

glucose concentrations and hemoglobin A1c levels. *Ann Intern Med* 2017;167:95–102

4. Beck RW, Connor CG, Mullen DM, Wesley DM, Bergenstal RM. The fallacy of average: how using HbA_{1c} alone to assess glycemic control can be misleading. *Diabetes Care* 2017;40:994–999
5. Malka R, Nathan DM, Higgins JM. Mechanistic modeling of hemoglobin glycation and red blood cell kinetics enables personalized diabetes monitoring. *Sci Transl Med* 2016;8:359ra130
6. Bergenstal RM. Glycemic variability and diabetes complications: does it matter? Simply put, there are better glycemic markers! *Diabetes Care* 2015;38:1615–1621
7. Bergenstal RM, Garg S, Weinzimer SA, et al. Safety of a hybrid closed-loop insulin delivery system in patients with type 1 diabetes. *JAMA* 2016;316:1407–1408

Understanding Continuous Glucose Monitoring Data

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Continuous glucose monitoring (CGM) systems are able to transmit glucose readings every 1–15 minutes to a receiver, insulin pump, phone(s), or watch, and eventually the glucose data may be uploaded to a computer, electronic medical record (EMR) system, and/or the Cloud.

After about a decade of many different, innovative CGM data reports being generated, often running to 20 or more printed pages, the Helmsley Charitable Trust supported a CGM data standardization consensus conference (1). The experts who convened modified an existing Ambulatory Glucose Profile (AGP) report (2) to arrive at a summary one-page report having three main elements: CGM metrics, an AGP modal day visualization, and a set of daily glucose profiles. In December 2017, two comprehensive consensus statements were published that agreed on definitions for core CGM metrics, priorities for routine display, and use of the AGP as the default glucose profile visualization (3,4).

Figure 1 is a sample AGP report that incorporates CGM metrics and a visual depiction that meet the consensus recommendations. There are many additional important CGM metrics and visualizations that can be helpful in clinical practice or research for a given patient or study.

CGM Metrics

Data Sufficiency. A recent study confirmed that 14 days of CGM data correlate well with 3 months of CGM data, particularly for mean glucose, time in range, and hyperglycemia measures (5). Within those 14 days, having at least 70% or ~10 days of CGM wear adds confidence that the data are a reliable indicator of usual patterns.

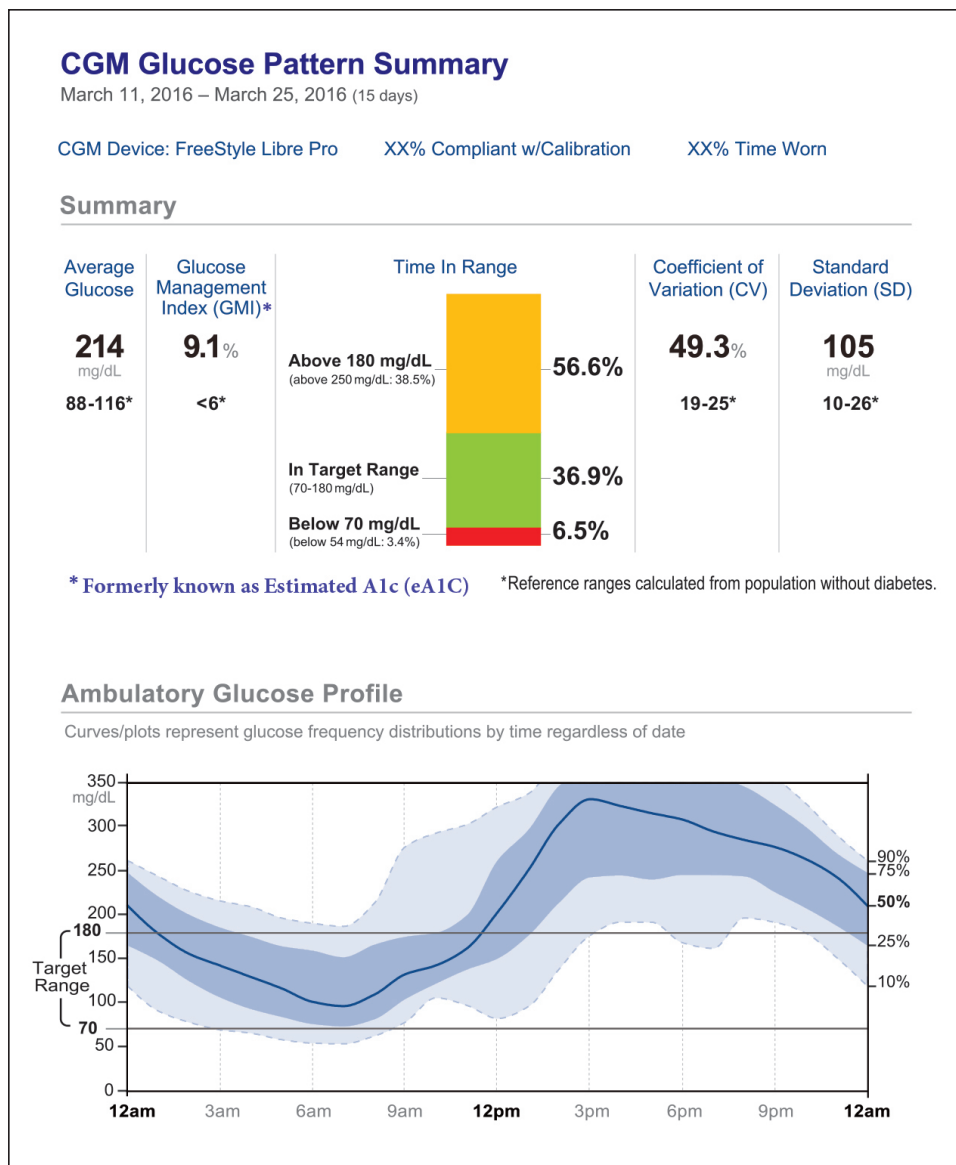
Average Glucose. The average glucose is highly correlated with A1C and measures of hyperglycemia but

not with glycemic variability or hypoglycemia. Used in isolation, it provides no insight into glucose patterns.

Glucose Management Index (GMI). This is the proposed term to replace “estimated A1C” (eA1C). For some time, the mean glucose value obtained from self-monitoring of blood glucose or, more reliably, CGM data has been used to estimate what an individual’s laboratory-measured A1C would be (and vice versa). Many clinicians and patients have found this a helpful metric to follow. Yet, there can be confusion for patients and clinicians when the laboratory A1C and the eA1C do not closely match. (See the article on p. 19 of this compendium for reasons they may not always match.) In the United States, there is now a requirement to replace “eA1C” with a new term that does not imply that the value is directly linked to the laboratory A1C value. The value is calculated from the mean CGM glucose similarly and reported in the same units. GMI is the name proposed to replace eA1C and is also intended to convey that this metric can be a helpful indicator of the need to address glucose management.

Time in Range (TIR). This is the CGM metric most commonly used as a guide to diabetes management. Collectively, there are now five agreed-upon, CGM-defined categories to quantitate the time a patient is spending with glucose values that are above, below, or in the target range. The time spent in each of these categories can be described as either the percentage of CGM glucose values or the number of minutes or hours per day spent in that category during the measurement period. For example, if half of all the CGM glucose readings over the 14 days are in the target range, TIR = 50% or 12 hours/day. The agreed-upon default TIR is 70–180 mg/dL, with the understanding that there may be circumstances in which the clinician or patient

FIGURE 1 Sample AGP report and interpretation notes



- There are adequate data to make an interpretation and action plan.
- Review of CGM metrics: note that average glucose, GMI (formerly known as eA1C), and measures of GV (CV and SD) are all very high and need attention. In addition, the TIR is low, and TIHyper and TIHypo are high enough to require action.
- The AGP alerts one to immediately address the hypoglycemia pattern between 6:00 and 9:00 a.m.
 - › Note that the glucose level drops steadily all night.
 - › Check the daily profiles to see if these patterns of hypoglycemia occur on any specific nights.
 - › Note the glucose is actually dropping from 3:00 p.m., with a rapid decline after dinner and likely at bedtime. Check on proper insulin dosing at dinner and bedtime and on evening events such as exercise that may lead to a drop in glucose.
- Once the hypoglycemia is minimized, address the rising glucose from 10:00 a.m. to 3:00 p.m.
 - › Mark waking and breakfast time to help determine whether the hyperglycemia is due to a rebound from hypoglycemia or related to waking or to eating breakfast or a snack without adequate insulin coverage.

Adapted from Fonseca V, Grunberger G. Standard glucose reporting: follow-up to the February 2016 AACE CGM consensus conference. *Endocr Pract* 2017;23:629–632.

wants to set an alternative target TIR (e.g., 70–140 mg/dL during the night for patients on hybrid closed-loop therapy).

Time in Hypoglycemia (TIIHypo). There are two CGM-defined cut points to define TIIHypo and one clinically defined hypoglycemia level.

- Level 1: Glucose <70 mg/dL and \geq 54 mg/dL, or 54–69 mg/dL
 - › Hypoglycemia alert level/low/need to monitor the situation
- Level 2: Glucose <54 mg/dL
 - › Clinically significant/very low/immediate action required
- Level 3. Severe hypoglycemia
 - › Altered mental and/or physical status requiring assistance

Levels <70 mg/dL are referred to as an alert for hypoglycemia and those <54 mg/dL indicate higher risk for individuals with known cardiovascular disease and are often associated with cognitive impairment. Glucose <54 mg/dL is emerging as the key level to assess when comparing drugs or treatment strategies in clinical trials.

Time in Hyperglycemia (TIIHyper). There are two CGM-defined cut points to define TIIHyper and one clinically defined hyperglycemia level.

- Level 1: Glucose >180 mg/dL and \leq 250 mg/dL, or 181–250 mg/dL
 - › Elevated or high glucose/need to monitor the situation
- Level 2: Glucose >250 mg/dL
 - › Clinically significant/very high/action required; consider correction insulin bolus, check insulin pump infusion set, increase hydration, address illness or excess stress if present, and consider checking urine or fingerstick ketones if persistent.
- Level 3: Diabetic ketoacidosis
 - › Ketones, acidosis, and usually hyperglycemia

It is important to note that no single metric of time in range (TIR, TIIHyper, or TIIHypo) can adequately characterize glucose control. An ideal CGM target is to maximize TIR with minimal TIIHypo.

Glucose Variability (GV). GV refers to how much the glucose reading varies from the mean or median glucose, the degree of up and down fluctuation (amplitude), and the frequency of variations (6). There are dozens of well-established GV metrics. Most measure the amplitude of GV, including coefficient of variation (CV), standard deviation (SD), interquartile range (IQR), and mean amplitude of glycemic excursion (MAGE). CV, consistently the most reliable GV marker, is not directly correlated with mean glucose or A1C. Current research shows that a CV value <36% represents low GV and a relatively stable glucose profile, whereas a CV value \geq 36% indicates an unstable glucose profile. SD is the most familiar GV measure and highly correlates with mean glucose and A1C. It is most reliable if glucose values are normally distributed around the

mean, which is rarely the case with CGM values. If the SD is less than the mean glucose divided by 3 (with the mean glucose being 120–180 mg/dL), it is reasonable to assume low GV and a stable glucose profile.

Interpreting AGP

Although the aforementioned glucose metrics are helpful in quantitating glucose control in a group or an individual, visualization of the 24-hour modal (or standard) day AGP report is emerging as an essential personalized management tool.

Figure 1 represents 14 daily glucose profiles collapsed to create a single AGP visual display. The solid line is the median or 50% line; half of all glucose values are above and half are below this value. The 25th and 75th percentile curves shaded in dark blue represent the interquartile range or 50% of all values and are a good visual indicator of the degree of GV. The dashed outer lines (the 10th to 90th percentile curves) indicate that only 10% of glucose readings were above or below these values over the 2-week period.

At a glance, clinicians and patients can determine the extent to which values are within the target range (70–180 mg/dL) and the times of day that pose potentially dangerous low or high patterns requiring immediate attention. The overall management goal is to make or keep the curve as narrow and flat as possible within the designated target range.

Following are tips for effective review of the AGP with patients to guide clinical decision making (7,8).

1. Make sure there are adequate data for decision making (see Data Sufficiency above).
2. Mark directly on the profile sheet:
 - Type and duration of diabetes, age, weight (kg), and, if on insulin, daily dose (units/kg)
 - Usual times for waking (W), breakfast (B), lunch (L), dinner (D), and bedtime (BT)
 - Medication time and doses directly under the curve at the time usually taken (This is a good time to emphasize how critical it is to take bolus insulin before meals.)
 - If there is a consistent time of exercise or snacking (which should also be marked below the curve)
3. Once the report is “marked up,” ask the patient to briefly describe and explain what he or she sees and why. Patients often provide honest, helpful insights to explain the glucose patterns.
4. Look for patterns of low glucose readings.
 - Remember, if the 10% lower line is touching the 70 mg/dL target line during a particular period of the day, 10% of all glucose values are <70 mg/dL at that time. Some action should be taken. If the 25% line is touching or below the 70 mg/dL target line or the 10% line reaches 54 mg/dL, immediate action is required.
 - Look at the separate printout of daily views to double-check patterns of low glucose and see if they are clustered on weekends or special activity days.

5. Look for patterns of high glucose values.
 - Remember to ask how many times per week a medication is forgotten or if insulin is actually taken before meals.
 - Look at your meal markers and discuss whether high values are before or after usual mealtimes.
 - Ask about usual differences in weekend versus weekday times for waking, meals, and bedtime.
 - Look at the separate printout of daily views to double-check patterns of high glucose and see if they are clustered on weekends or special activity days.
6. Discuss areas where dark blue (50% of values) or light blue (80% of values) shaded areas are very wide (corresponding to high GV).
 - Can the patient do anything to reduce GV by adjusting the timing or amount of food intake, carbohydrate counting, timing of medications, exercise times or amounts, and/or stress?
 - Match food and exercise log or electronic data, if available, with AGP.
7. Compare current AGP and CGM metrics to those from last visit (or contact), if available, and discuss progress.
8. Agree on an action plan consisting of one or two recommendations:
 - Always treat hypoglycemia first.
 - When treating a pattern of hyperglycemia, look at least 12–18 hours past the time of the hyperglycemia you plan to treat. If the solid or light blue curves are touching the 70 mg/dL line or lower, be very conservative or hold off on correcting hyperglycemia until the hypoglycemia is addressed.

9. Print a copy of the marked-up AGP for the patient, and enter the AGP into the EMR, if possible, or at least copy and paste the AGP into the EMR progress note.

REFERENCES

1. Bergenstal RM, Ahmann AJ, Bailey T, et al. Recommendations for standardizing glucose reporting and analysis to optimize clinical decision making in diabetes: the Ambulatory Glucose Profile (AGP). *Diabetes Technol Ther* 2013;15:198–211
2. Mazze RS, Lucido D, Langer O, Hartmann K, Rodbard D. Ambulatory glucose profile: representation of verified self-monitored blood glucose data. *Diabetes Care* 1987;10:111–117
3. Danne T, Nimri R, Battelino T, et al. International consensus on use of continuous glucose monitoring. *Diabetes Care* 2017;40:1631–1640
4. Agiostratidou G, Anhalt H, Ball D, et al. Standardizing clinically meaningful outcome measures beyond HbA1c for type 1 diabetes: a consensus report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. *Diabetes Care* 2017;40:1622–1630
5. Riddlesworth TD, Beck RW, Gal RL, et al. Optimal sampling duration for continuous glucose monitoring to determine long-term glycemic control. *Diabetes Technol Ther* 2018;20:314–316
6. Kovatchev B, Cobelli C. Glucose variability: timing, risk analysis, and relationship to hypoglycemia in diabetes. *Diabetes Care* 2016;39:502–510
7. Carlson AL, Mullen DM, Bergenstal RM. Clinical use of continuous glucose monitoring in adults with type 2 diabetes. *Diabetes Technol Ther* 2017;19(Suppl. 2):S4–S11
8. Hirsch IB, Verderese CA. Professional flash continuous glucose monitoring with ambulatory glucose profile reporting to supplement A1C: rationale and practical implementation. *Endocr Pract* 2017;23:1333–1344