Continuous Glucose Monitoring Data as an Adjunct to A1C

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A1C remains an established risk marker for population health and is used extensively in clinical research and regulatory trials. However, factors such as hemoglobinopathies and heritable differences in glycation dynamics can render A1C less useful as a guide to glycemic control for some patients (1). The health care improvement goal of excellent quality and patient experience at reasonable cost is further shifting emphasis away from A1C as the reigning standard of care toward minimizing the daily burdens of living with diabetes. Indeed, many experts contend that it is time to formalize a definition of optimal control that includes A1C being at target (personalized for each individual, but usually ~7% for most adults) without occurrence of severe hypoglycemia and with only a minimal number of very low or clinically significant low glucose values (2).

Yet A1C, even in combination with the rate of hypoglycemia, still has some inherent barriers to being an ideal personal management guide. First, A1C represents an average glucose level over 2–3 months and, as such, is unable to reveal potentially dangerous episodes of hypoglycemia or hyperglycemia. Second, individuals with the same mean glucose (derived through continuous glucose monitoring [CGM]) may have a clinically significant variation in their laboratory-measured A1C. In practice, this means that a laboratory-measured A1C of 8% may have a CGM-derived mean glucose ranging from 155 to 218 mg/dL, obviously with different clinical management implications. Variation in the relationship between A1C and mean glucose has been observed between races and to an even greater extent between individuals of the same race (3,4). Although the mechanisms for individual variation in the relationship of A1C to mean glucose are still being investigated, inherent differences in the rate of hemoglobin glycation and red blood cell life span remain the leading hypothesis (5).

With several excellent approved CGM systems available, including many that are factory-calibrated, and given the fact that current CGM metrics and glucose profile visualizations are mostly standardized (see the article on p. 20 of this compendium), it is now feasible to define glucose control and management decisions based on CGM data and reports. A key patient-centered metric is to have as many glucose values as possible fall within the individualized target range, referred to as time in target range or simply time in range (TIR), with the common default range of 70–180 mg/dL. The more TIR the better the A1C is likely to be because these two variables are highly correlated. For optimal management, patients should have a TIR level as high as possible with a very low level of time in hypoglycemia (TIHypo). Maximal TIR with minimal TIHypo is a reasonable overarching glycemic target (6).

Below are two ways to assess the correlation of CGM-derived TIR data and A1C laboratory data.

1. Consider the mean TIR, achieved using the most advanced currently approved technology (hybrid closed-loop therapy), of 124 individuals with type 1 diabetes who had a mean A1C of 6.9% (secondary analysis of data from Bergenstal et al. [7]).
   - TIR (70–180 mg/dL) ~72% or 17.3 hours/day
   - TIHypo (<70 mg/dL) ~3% or 43 min/day (<1% or ~14 min/day of this <54 mg/dL)
   - TIHyper (time in hyperglycemia; >180 mg/dL) ~25% or 6 hours/day (<6% or ~86 min/day of this >250 mg/dL)

2. Consider the correlations of TIR and A1C achieved from an analysis of several hundred people with type 1 or type 2 diabetes in a series of clinical trials (Table 1) (secondary analysis of data from Beck et al. [4]; R. Beck, personal communication).

TABLE 1 Correlations of TIR and A1C Achieved from an Analysis of Several Hundred People with Type 1 or Type 2 diabetes (4)

Measured TIR (70–180 mg/dL)	A1C	95% CI
40%	8.1%	7.1–9.1%
50%	7.7%	6.7–8.7%
60%	7.3%	6.3–8.3%
70%	6.9%	5.9–7.9%
80%	6.5%	5.5–7.5%

In summary, laboratory-derived A1C is a measure of population health and of long-term risk for diabetes complications but is not an individualized management tool. An elevated A1C implies that action is needed but does not help tailor treatment because neither hypoglycemia, glucose variability, nor timing of hyperglycemia are revealed by this average glucose measure. In contrast, a standardized Ambulatory Glucose Profile (AGP) report clearly shows dangerous high or low patterns that need immediate attention. The timing and magnitude of hyperglycemia, hypoglycemia, and glucose variability are clearly visualized in the AGP and quantitated by CGM metrics (TIR, TIHypo, TIHyper, and coefficient of variation/standard

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