



Time in Range: How to Measure It, How to Report It, and Its Practical Application in Clinical Decision-Making

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The A1C metric has been the gold standard for assessing glycemia for decades. This biologic assay, based on averaging, is fraught with limitations and may be giving way to more holistic approaches. This article reviews glycemic time in range as the new standard for assessing patients with continuous glucose monitoring data. Information from the International Consensus Group on Time in Range will be summarized.

Evolution of A1C as the Gold Standard for Glycemia

A1C has been the most common biomarker for determining blood glucose control among individuals with diabetes since its discovery in the 1960s by Rahbar et al. (1). Although results from the landmark Diabetes Control and Complications Trial (DCCT) (2) and U.K. Prospective Diabetes Study (3) reported more than two decades ago demonstrated that reductions in A1C lead to fewer short- and long-term microvascular complications and less long-term macrovascular disease (2–4), standardization of laboratory methods and consensus for target goals would take several more years to develop (5). In 2011, the World Health Organization released a report recommending A1C as a diagnostic test for diabetes provided that specific clinical and quality criteria were met (6). Because of its reliability, relative ease to obtain, and low cost to perform (7), A1C is widely accepted as the gold standard for determining blood glucose control over the previous 2–3 months and for assessing risk for diabetes-related microvascular outcomes.

Despite its popularity, however, a lack of consistency in characterizing chronic glycemia (reported as a percentage of glycated hemoglobin) and acute glucose levels

monitored on a day-to-day basis (reported as milligrams per deciliter or millimoles per liter) led to confusion among both patients and health care providers (HCPs) (8). Subsequently, the relationship between A1C and average glucose was determined in the A1C-Derived Average Glucose study (9), which assisted people with diabetes and their clinicians in setting realistic blood glucose monitoring (BGM) targets to achieve individualized A1C goals (10).

Limitations of the A1C Metric

Although the correlation between A1C and average glucose can be useful in setting objective targets, there remain notable limitations. One of the main limitations of A1C is its inability to represent acute glycemic excursions (11). Additionally, A1C can be subject to variations in accuracy in patients with anemia, specific hemoglobinopathies, iron deficiency, pregnancy, and hepatic disease, and it can vary among different racial and ethnic groups (12).

It is important to note that the overall value of A1C should not be discounted; it still provides a relevant means of assessing overall blood glucose control and is correlated with the development of chronic complications. When used in combination with continuous glucose monitoring (CGM), a more accurate depiction of both acute and chronic glycemic control can be ascertained (13).

New Terminology: Glucose Management Index

In the early stages of developing metrics for how CGM data should be reported, the term “estimated A1C” (eA1C) was used to provide clinicians and patients with an approximate value of a simultaneously measured laboratory A1C. Although many HCPs and people with diabetes found this helpful in the clinical practice setting, confusion

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and frustration arose when the CGM-derived eA1C and laboratory-measured A1C did not closely correlate (14).

If the average glucose while wearing a CGM sensor remains constant for 90 days, the eA1C and laboratory A1C will match more closely. However, such constant average glucose may not always be the case. Based on our clinical experience, patients frequently make healthier lifestyle choices and more closely follow their medication regimens while using a CGM system. If someone is using CGM for only a 10- to 14-day period within the 90 days covered by the A1C test, the eA1C during the CGM wear period may be lower than their true A1C because of increased patient vigilance. On the other hand, if a patient is acutely ill or has increased stress while wearing a CGM sensor, the eA1C may be higher than their true A1C. Furthermore, differences in red blood cell turnover and glycation rates can also lead to incongruencies between eA1C and laboratory-measured A1C.

Based on concerns of the U.S. Food and Drug Administration and feedback from many diabetes HCPs, novel terminology was adopted to replace the eA1C. This led to the development and refinement of the term “glucose management indicator” (GMI). Bergenstal et al. (14) argued that, because GMI is based on the average CGM results for the period, it provides an indication of the current state of a patient’s glucose management. At the time of this publication, the GMI has replaced eA1C on CGM reports.

Inevitably and expectedly, there will continue to be clinical scenarios in which GMI and A1C do not match. In these situations, it will be crucial to keep the patient’s safety in mind when setting therapeutic targets to achieve the desired outcomes. It is prudent for HCPs to evaluate A1C and GMI as only individual pieces of a complete puzzle when it comes to the full assessment of glycemic control. Notably, because GMI is derived from the measured glucose levels, it may not be subject to the previously discussed limitations of laboratory-measured A1C.

Complexities of Glucose Dynamics Independent of A1C: Glycemic Variability

Because of the limitations of A1C, the search has continued for alternative ways to measure and assess blood glucose fluctuations. Glycemic variability (GV) is an indicator of hyper- and hypoglycemia that takes into consideration both the amplitude of the excursion (how far out of range a blood glucose measurement is) and the time spent in the excursion (how long the blood glucose is out of range) (15,16).

To demonstrate this concept, visualize two patients: one with blood glucose values ranging from 100 to 200 mg/dL

and the other with blood glucose levels of 50–250 mg/dL. Both patients have an average blood glucose of 150 mg/dL, and both have the same A1C. Most would agree that the patient with glucose values from 100 to 200 mg/dL has overall safer glycemic control. This patient has smaller glycemic excursions and, therefore, a lower GV.

Unfortunately, there is no universally accepted marker for GV. The Advanced Technologies & Treatments for Diabetes (ATTD) Congress International Consensus on Use of Continuous Glucose Monitoring recommends the use of coefficient of variation (CV), which is simply defined as the SD divided by the mean and multiplied by 100 (reported as a percentage), as the primary indicator for GV because it is more sensitive to hypoglycemia than SD alone (11). Although this marker considers the amplitude of GV, it does not reflect the time spent in glycemic excursions. Time in range (TIR), discussed in depth later, more accurately depicts the time component of GV (16).

Large glucose fluctuations may increase oxidative stress and inflammation, which in turn cause endothelial cell damage (17). Although the effect of GV on microvascular complications is controversial, several studies have linked glucose excursions with increased cardiovascular risk, decline in cognitive function, and reduced quality of life (18–20). GV is quickly becoming an independent risk factor for cardiovascular mortality in patients with diabetes (17). High GV may also be a risk factor for hypoglycemia. To limit the risk of hypoglycemia while reducing A1C, GV must be decreased (15,16).

Frequency and Severity of Hypoglycemia in Type 2 Diabetes Irrespective of A1C

Hypoglycemia, generally categorized by the American Diabetes Association (ADA) (21) as level 1 (blood glucose ≥ 54 and < 70 mg/dL), level 2 (blood glucose < 54 mg/dL), or level 3 (severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia) may occur in up to 50% of people with type 2 diabetes and is associated with multiple safety concerns and unfavorable health outcomes (22). Hypoglycemia not only increases the risk of falls, fall-related fractures, and cardiovascular events, but also increases the risk for dementia and ultimately leads to poor health-related quality of life and increased mortality (23–28).

If all agree that minimizing hypoglycemia should be a focus, the issue then shifts to identifying those at highest risk. Landmark diabetes trials have consistently shown that intensive glucose control strategies are associated with higher rates of hypoglycemia (29,30); however,

conflicting evidence exists regarding the correlation between A1C and risk for hypoglycemia. The DCCT found an inverse relationship between A1C and severe hypoglycemia in people with type 1 diabetes, indicating that those with lower A1C levels are at higher risk for hypoglycemia and its subsequent risks and complications (2). In contrast, a post hoc analysis of the Action to Control Cardiovascular Risks in Diabetes (ACCORD) trial found that those with poor diabetic control, as evidenced by higher A1C levels, were at increased risk for hypoglycemia (31). The ACCORD trial included patients with established type 2 diabetes and either established cardiovascular disease (CVD) or at high risk for CVD. The Diabetes and Aging Study of >9,000 patients with type 2 diabetes added to the controversy. Although patients with an A1C <6 or $\geq 9\%$ were at highest risk for self-reported, severe hypoglycemia, hypoglycemia was observed at all levels of A1C and glycemic control (23).

Experts recommend using shared decision-making when choosing A1C goals, and it is common practice to aim for a less stringent A1C goal for patients who are >65 years of age (21). However, evidence suggests that less stringent A1C goals may not lower rates of hypoglycemia, which is the primary safety risk in this patient population. A study published in 2017 by Munshi et al. (32) found no difference in the risk for hypoglycemia based on measured A1C in patients >65 years of age with type 2 diabetes. Furthermore, the Diabetes and Aging Study found that age, duration of diabetes, or diabetes pharmacologic treatment class did not affect the relative risk of hypoglycemia at different A1C levels (23).

Evolution of Glycemic Targets

Ultimately, hypoglycemia is a frequent risk, and we should consider its consequences for all patients with diabetes regardless of their A1C. In 2020, the ADA stated that glycemic control is best evaluated by a combination of A1C and BGM or CGM, especially in patients with high GV (32). The TIR metric is readily available with the use of CGM and is generally defined as the percentage of time glucose is within a predetermined target range. TIR may provide a more accurate assessment of glycemic stability and hypoglycemia, thereby helping clinicians mitigate associated risks in all patients with diabetes.

2017 ATTD Consensus

In 2017, the ATTD Congress organized an international panel of individuals with diabetes, clinicians, and researchers with expertise in CGM to develop standardized

CGM metrics (11). Although each clinically significant metric (described in Table 1) can be used to evaluate glycemic control, the consensus panel identified TIR as the specific metric to use to guide therapeutic decision-making over A1C alone. The standardization of TIR categories and the definition of other CGM core metrics would allow for the effective interpretation of CGM data to optimize clinical outcomes. Subsequently, five distinct TIR categories were defined as follows:

1. Time below range (TBR) level 2: very low
2. TBR level 1: low
3. TIR
4. Time above range (TAR) level 1: high
5. TAR level 2: very high

Although individual target ranges vary, TIR is most commonly defined as blood glucose levels between 70 and 180 mg/dL. This range accounts for the defined thresholds of hypoglycemia and peak postprandial glucose levels (32). TBR and TAR are subdivided into two levels each based on severity, with level 2 being the most extreme cases of hypo- and hyperglycemia, respectively. For example, blood glucose levels <54 mg/dL have been linked to decreased hypoglycemia awareness and impaired neurologic function, which may require assistance from others, and increased mortality (33,34); blood glucose levels >250 mg/dL have been associated with increased risk for diabetic ketoacidosis and long-term complications (34). The levels for TBR and TAR should be used to help determine the urgency of clinical response. Based on ATTD consensus recommendations, HCPs should monitor and take action if needed for level 1 hypoglycemia or level 1 hyperglycemia. For level 2 excursions, immediate action is required (11).

2019 ATTD Consensus

In 2019, an ATTD Congress panel met again to define specific clinical targets for the previously determined CGM metrics. The group reached consensus targets for glycemic cut points and time per day (expressed as a percentage of CGM readings and minutes/hour) not only in individuals with type 1 or type 2 diabetes, but also in other populations, including pregnant women with diabetes and older/high-risk patients. Primary care providers treat the vast majority of patients with type 2 diabetes, and the target ranges and time goals defined for these patients are as follows (35):

1. TBR level 2 (very low): <54 mg/dL and <1%
2. TBR level 1 (low): 54–69 mg/dL and <4%
3. TIR: 70–180 mg/dL and >70%

TABLE 1 Standardized CGM Metrics and Respective Targets on the AGP for Patients With Type 1 or Type 2 Diabetes

| Metric | Targets/Goals | |
|---------------------------------|------------------------|--------------------------|
| | Standard-Risk Patients | Older/High-Risk Patients |
| Days CGM is worn, <i>n</i> | | 10–14 |
| Amount of time CGM is active, % | | ≥70 |
| Average glucose, mg/dL* | 154 | 183 |
| GMI, %* | <7 | <8 |
| GV, %CV | | ≤36 |
| Times in defined ranges, % | | |
| TAR level 2: >250 mg/dL | <5 | <10 |
| TAR level 1: >180 mg/dL | <25 | <50 |
| TIR: 70–180 mg/dL | >70 | >50 |
| TBR level 1: <70 mg/dL | <4 | <1 |
| TBR level 2: <54 mg/dL | <1 | 0 |

*Based on A1C goals for designated patient populations.

4. TAR level 1 (high): 181–250 mg/dL and <25%
5. TAR level 2 (very high): >250 mg/dL and <5%

Target ranges and time goals should be adjusted based on the population being treated. For example, older patients and those at higher risk of hypoglycemia have higher TAR goals and lower TBR goals as shown in Table 1.

Relationship Between TIR and A1C

TIR assesses glucose control over a period of hours to days. In comparison, A1C assesses average glucose over a period of 8–12 weeks. Although we know that TIR is inversely correlated with A1C (i.e., as TIR increases, A1C decreases and vice versa) (36), the extent of the correlation between TIR and A1C is not fully apparent. A retrospective analysis of 18 articles with paired A1C and TIR metrics found that, for every ~10% change in TIR, there was an inverse change of ~0.8% in A1C (37). In contrast, a study looking at the relationship between TIR and A1C in patients with type 1 diabetes showed a wider and weaker correlation (36).

Overall, robust data are still lacking for the correlation between CGM metrics and clinical outcomes. However, recent studies have suggested correlations between TIR and diabetes complications regardless of A1C. A study by Lu et al. (38) involving >3,000 patients found that those with a lower TIR and higher GV experienced more advanced diabetic retinopathy (38). Another study by Guo et al. (39) assessing the association of TIR and diabetic cardiovascular autonomic neuropathy found that lower TIR was significantly associated with more severe neuropathy independent of A1C. Moreover, a post hoc analysis of data from the DCCT estimated TIR based on

serial blood glucose tests completed seven times per day. (CGM was not available during the DCCT.) Using this method, overall mean TIR for the 1,440 participants was 41%; for every 10% decrease in TIR, the hazard ratio for retinopathy progression increased by 64%, and the hazard ratio for microalbuminuria increased by 40% (40). Overall, lower TIR appears to be associated with increased risk for microvascular complications. Whereas the DCCT involved patients with type 1 diabetes, it is unknown whether these findings can be extrapolated to patients with type 2 diabetes, and more data evaluating these potential associations may be needed.

Standardization of TIR

When evaluating and taking actions based on CGM reports, clinicians should aim to increase patients' overall TIR. There are different strategies one can take to achieve this goal, including focusing on decreasing TBR or on decreasing TAR. Like Battelino et al. (35), we suggest initially targeting a reduction in TBR to reduce hypoglycemia and related complications. To decrease TBR, clinicians and patients should have open conversations to determine the causes of hypoglycemia; medication doses may need to be lowered or medications may need to be changed altogether. According to national experts, the medication classes preferred when there is a need to minimize hypoglycemia include dipeptidyl peptidase-4 inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, sodium–glucose cotransporter 2 (SGLT2) inhibitors, and thiazolidinediones (41). Furthermore, SGLT2 inhibitors and GLP-1 receptor agonists have demonstrated an ability to increase TIR in clinical trials

(42,43). After addressing TBR, the focus can shift to reducing TAR through improved therapeutic lifestyle choices and optimized pharmacologic management.

Using TIR in Clinical Practice

We are not suggesting that TIR replace A1C as the sole marker for glycemic control. To comprehensively evaluate glycemic control requires an understanding of the diurnal glucose patterns that underlie TIR and characterize A1C. This understanding requires that TIR and A1C be evaluated in the context of the ambulatory glucose profile (AGP) CGM report (44). Although other methods have been published for interpreting the AGP (45), we use the approach outlined by Mazze and Cranston (44) to guide our strategy, which is summarized in the following five steps:

1. Evaluate data adequacy
2. Identify and address TBR
3. Identify and address high GV
4. Identify and address TAR
5. Improve TIR

Case Study 1

J.B. is a 67-year-old man with type 2 diabetes and has a significant medical history that includes dyslipidemia, hypertension, morbid obesity (BMI 40 kg/m²), obstructive sleep apnea, vitamin D deficiency, and estimated glomerular filtration rate (eGFR) >59 mL/min/1.73 m². He is taking metformin extended release 1,000 mg twice daily and subcutaneous dulaglutide 1.5 mg weekly. His current A1C of 7.6% has increased from his most recent previous value of 6.5%. According to J.B., this increase was likely the result of “eating more over the holidays” but he has recently “gotten back on track” with his diet.

According to his AGP report (Figure 1), J.B. has worn his CGM sensor for a duration of 15 days with the CGM active 100% of the time, providing adequate data for decision-making. His average glucose is 149 mg/dL, GMI is 6.9%, and GV is 15.2%. His TIR is 89%, TBR level 1 is 0%, TBR level 2 is 0%, TAR level 1 is 11%, and TAR level 2 is 0%. There are no observed patterns of low glucose levels (<70 mg/dL) according to the AGP and the daily glucose profiles shown at the bottom of the report. He appears to have mildly elevated glucose levels from about 9:00 a.m. to noon and again from about 9:00 to 11:00 p.m.

Based on the patient’s age and current comorbidities, it would be reasonable to set his A1C goal as <7%, per ADA

guidelines (21). Judging from his AGP report, J.B. seems to have better blood glucose control than his most recent A1C would indicate based on his average glucose and GMI. He is currently meeting his goals for TIR (>70%), TBR level 1 (<4%), TBR level 2 (<1%), TAR level 1 (<25%), and TAR level 2 (<5%).

A reasonable action plan based on this report would be to continue his current diabetes medication regimen and lifestyle and dietary habits. Further discussion could focus on identifying trends in postprandial elevations that have been occurring midmorning and in the evenings. Often, there is room for further improvement, so the clinician could recommend to the patient that he consider reducing his carbohydrate intake around those mealtimes. Overall, this patient appears to be on the right track to attaining an improved A1C when it is next measured assuming he maintains his current blood glucose profile.

Case Study 2

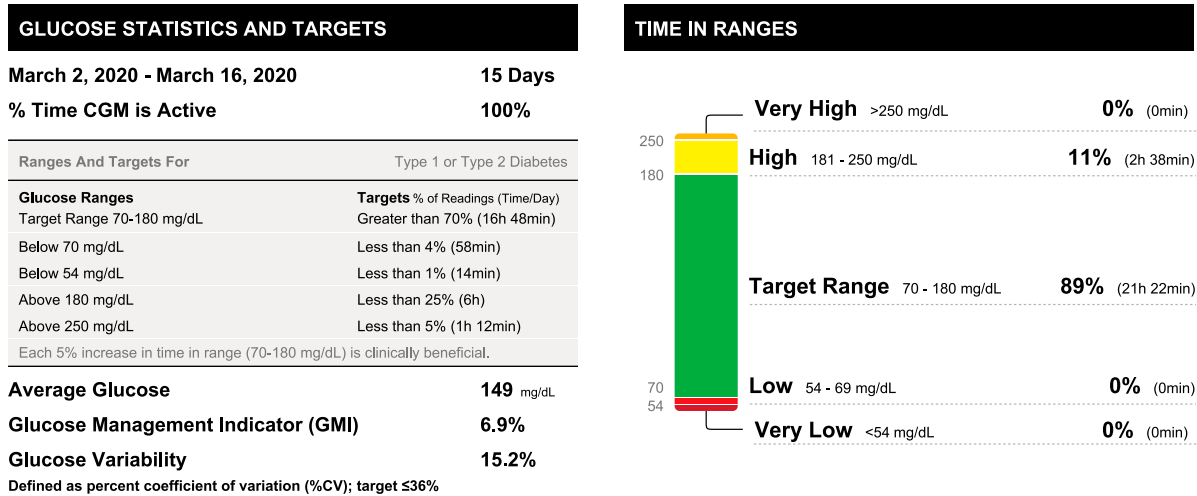
R.F. is a 73-year-old man with type 2 diabetes and has a significant medical history that includes dyslipidemia, hypertension, obesity (BMI 33 kg/m²), obstructive sleep apnea, CKD stage 4 (eGFR 19 mL/min/1.73 m²), and gout. He is on a mixed NPH/regular insulin (70/30) regimen of 50 units before breakfast and 50 units before dinner, plus an additional 10 units if he is eating a “larger meal.” He describes adding extra insulin ~50% of the time. His current A1C of 9% has decreased from his most recent previous value of 12.3%.

According to his AGP report (Figure 2), he has worn his CGM sensor for a duration of 15 days with the CGM active 100% of the time, providing adequate data for decision-making. His average glucose is 141 mg/dL, GMI is 6.7%, and GV is 54.5%. His TIR is 54%, TBR level 1 is 5%, TBR level 2 is 14%, TAR level 1 is 20%, and TAR level 2 is 7%. There is a repeated pattern of low glucose levels (<70 mg/dL) between about 6:00 and 9:00 a.m. as shown on the AGP and the daily glucose profiles at the bottom of the report. He also has a pattern of elevated glucose levels (>180 mg/dL) from about 1:00 to 4:00 p.m.

Based on the patient’s age and current comorbidities, it would be reasonable to set his A1C goal at <7.5% per ADA guidelines (21). Judging from his AGP report, R.F. seems to have better blood glucose control than his most recent A1C would indicate based on his average glucose and GMI. However, he is only meeting his goal of TAR level 1 (<25%). His elevated GV (goal ≤36%) and below-goal TIR show wide variations of GV and put him at an increased risk for diabetes-related complications (38–40).

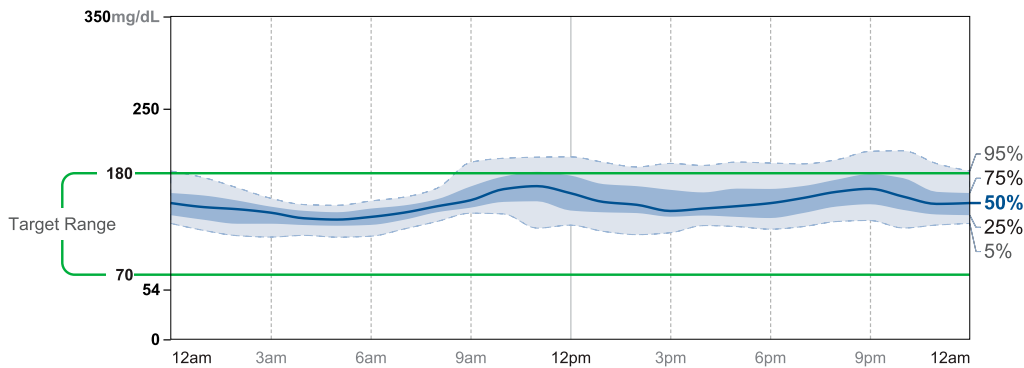
AGP Report

March 2, 2020 - March 16, 2020 (15 Days)



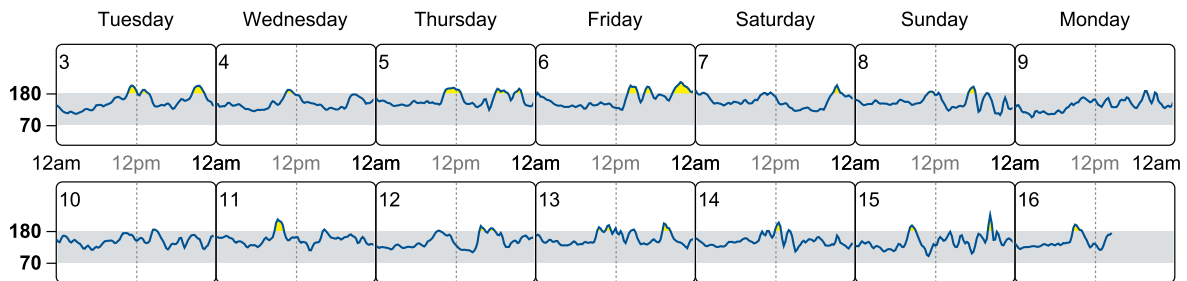
AMBULATORY GLUCOSE PROFILE (AGP)

AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if occurring in a single day.



DAILY GLUCOSE PROFILES

Each daily profile represents a midnight to midnight period with the date displayed in the upper left corner.



Source: Battellino, Tadej, et al. "Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range." Diabetes Care, American Diabetes Association, 7 June 2019, <https://doi.org/10.2337/dci19-0028>.

FIGURE 1 AGP report for patient J.B. in case study 1.

A reasonable action plan based on this report would be to first reduce or eliminate his TBR. Because of cost considerations, we are unable to change him to a true basal-bolus insulin regimen. Using his current insulin

therapy, it would be reasonable to decrease his evening dose to attempt to reduce his early-morning hypoglycemia and continue his morning insulin dose as it is at this time. Further discussion could focus on the postprandial elevation trend

AGP Report

February 19, 2020 - March 4, 2020 (15 Days)

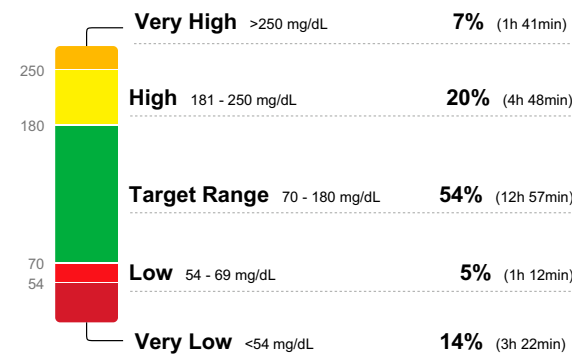
GLUCOSE STATISTICS AND TARGETS

February 19, 2020 - March 4, 2020 **15 Days**
% Time CGM is Active **100%**

| Ranges And Targets For | | Type 1 or Type 2 Diabetes |
|--|--|---|
| Glucose Ranges | | Targets % of Readings (Time/Day) |
| Target Range 70-180 mg/dL | | Greater than 70% (16h 48min) |
| Below 70 mg/dL | | Less than 4% (58min) |
| Below 54 mg/dL | | Less than 1% (14min) |
| Above 180 mg/dL | | Less than 25% (6h) |
| Above 250 mg/dL | | Less than 5% (1h 12min) |
| Each 5% increase in time in range (70-180 mg/dL) is clinically beneficial. | | |

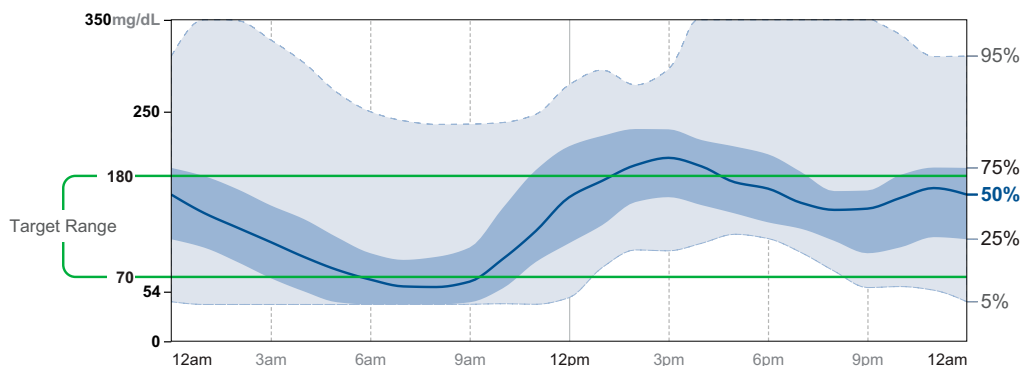
Average Glucose **141 mg/dL**
Glucose Management Indicator (GMI) **6.7%**
Glucose Variability **54.5%**
 Defined as percent coefficient of variation (%CV); target ≤36%

TIME IN RANGES



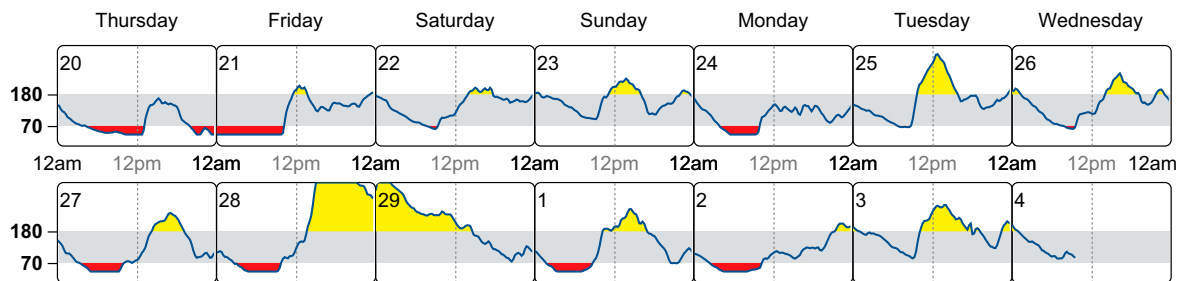
AMBULATORY GLUCOSE PROFILE (AGP)

AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if occurring in a single day.



DAILY GLUCOSE PROFILES

Each daily profile represents a midnight to midnight period with the date displayed in the upper left corner.



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FIGURE 2 AGP report for patient R.F. in case study 2.

that is occurring in early to late afternoon. The clinician could suggest that he consider reducing his carbohydrate intake in the mornings. Once R.F.'s TBR decreases, we can then focus at future visits on reducing his TAR and GV.

The Added Value of TIR for Decision-Making

The patients in the two case studies above have similar average glucose and GMI values on their AGP reports. If one were to evaluate based on A1C alone (in the absence

of BGM results), it would be reasonable to hypothesize that R.F., the patient in case study 2, in particular, had a dramatic enough improvement in A1C to warrant continuing his current insulin regimen in hopes of further improvements at his next A1C. However, his CGM data and AGP report reveal a much different clinical picture, in which it is clear that he is experiencing elevated GV and episodes of overnight hypoglycemia. Although R.F.'s GMI and average glucose appear to be acceptable (and are even better than those of J.B., the patient in case study 1), in the context of TIR metrics, his blood glucose is not ideally controlled. Based on the more complete picture of his blood glucose profile provided from his AGP report, we are able to make a more informed and safer decision to adjust his insulin doses and are thus more likely to lower his A1C without causing undue hypoglycemia.

Conclusion

The case studies presented above demonstrate the added benefit of assessing TIR and its impact in facilitating the development of safe and effective care plans for patients with diabetes. When TIR and A1C are considered together, HCPs can more accurately assess patients' day-to-day GV and hypoglycemia risk and help them minimize long-term microvascular and macrovascular complications.

We recommend that primary care providers follow published methods for evaluating AGP reports and adhere to the TBR, TIR, and TAR goals as recommended by the ATTD Congress consensus panel. Although evaluating CGM data and reviewing AGP reports may seem intimidating at first, we believe this technology can be safely incorporated into the primary care setting, and we foresee CGM, and specifically TIR, becoming a new (and better) standard marker for glycemic control.

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DUALITY OF INTEREST

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Ingelheim/Lilly, Mannkind/Merck Diabetes, and Sanofi/Voluntis; and has been a consultant for Abbott Diabetes Care/AstraZeneca, Bayer Cardio Renal, Boehringer Ingelheim/Lilly, and Sanofi/Voluntis. D.K.F. has served on a speaker's bureau for Janssen Pharmaceuticals. No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

E.E.W. and W.J.G. researched data, contributed to writing the manuscript, and reviewed and edited the manuscript. K.M. and D.K.F. researched data and wrote the manuscript. N.W. reviewed and edited the manuscript. E.E.W. is the guarantor of this work and, as such, had full access to all the sections of the manuscript and references and takes responsibility for the integrity and accuracy of this review.

REFERENCES

1. Rahbar S, Blumenfeld O, Ranney HM. Studies of an unusual hemoglobin in patients with diabetes mellitus. *Biochem Biophys Res Commun* 1969;36:838-843
2. Nathan DM, Genuth S, Lachin J, et al.; Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977-986
3. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-853
4. Lachin JM, Genuth S, Cleary P, Davis MD, Nathan DM; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *N Engl J Med* 2000;342:381-389
5. Gillery P. A history of HbA1c through *Clinical Chemistry and Laboratory Medicine*. *Clin Chem Lab Med* 2013;51:65-74
6. World Health Organization. *Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus. Abbreviated Report of a WHO Consultation*. Geneva, Switzerland, World Health Organization, 2011
7. Gupta S, Jain U, Chauhan N. Laboratory diagnosis of HbA1c: a review. *J Nanomed Res* 2017;5:00120
8. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ; A1c-Derived Average Glucose Study Group. Translating the A1C assay into estimated average glucose values. *Diabetes Care* 2008;31:1473-1478
9. Lenters-Westra E, Slingerland RJ. Hemoglobin A1c determination in the A1C-Derived Average Glucose (ADAG) study. *Clin Chem Lab Med* 2008;46:1617-1623
10. Klonoff DC. ADAG study group data links A1C levels with empirically measured blood glucose values: new treatment guidelines will now be needed. *J Diabetes Sci Technol* 2014;8:439-443
11. Danne T, Nimri R, Battelino T, et al. International consensus on use of continuous glucose monitoring. *Diabetes Care* 2017;40:1631-1640

12. Jia W. Standardising HbA_{1c}-based diabetes diagnosis: opportunities and challenges. *Expert Rev Mol Diagn* 2016;16:343–355
13. Chehregosha H, Khamseh ME, Malek M, Hosseinpanah F, Ismail-Beigi F. A view beyond HbA_{1c}: role of continuous glucose monitoring. *Diabetes Ther* 2019;10:853–863
14. Bergenstal RM, Beck RW, Close KL, et al. Glucose management indicator (GMI): a new term for estimating A1C from continuous glucose monitoring. *Diabetes Care* 2018;41:2275–2280
15. Kovatchev BP. Metrics for glycaemic control: from HbA_{1c} to continuous glucose monitoring. *Nat Rev Endocrinol* 2017;13:425–436
16. Kovatchev B. Glycemic variability: risk factors, assessment, and control. *J Diabetes Sci Technol* 2019;13:627–635
17. Ceriello A, Monnier L, Owens D. Glycaemic variability in diabetes: clinical and therapeutic implications. *Lancet Diabetes Endocrinol* 2019;7:221–230
18. Temelkova-Kurktschiev TS, Koehler C, Henkel E, Leonhardt W, Fuecker K, Hanefeld M. Postchallenge plasma glucose and glycemic spikes are more strongly associated with atherosclerosis than fasting glucose or HbA_{1c} level. *Diabetes Care* 2000;23:1830–1834
19. Haffner S. The importance of postprandial hyperglycaemia in development of cardiovascular disease in people with diabetes: point. *Int J Clin Pract Suppl* 2001;123:24–26
20. Cox D, Gonder-Frederick L, McCall A, Kovatchev B, Clarke W. The effects of glucose fluctuation on cognitive function and QOL: the functional costs of hypoglycaemia and hyperglycaemia among adults with type 1 or type 2 diabetes. *Int J Clin Pract Suppl* 2002;129:20–26
21. American Diabetes Association. 6. Glycemic targets: *Standards of Medical Care in Diabetes—2020*. *Diabetes Care* 2020;43(Suppl. 1):S66–S76
22. Edridge CL, Dunkley AJ, Bodicoat DH, et al. Prevalence and incidence of hypoglycaemia in 532,542 people with type 2 diabetes on oral therapies and insulin: a systematic review and meta-analysis of population based studies. *PLoS One* 2015;10:e0126427
23. Lipska KJ, Warton EM, Huang ES, et al. HbA_{1c} and risk of severe hypoglycemia in type 2 diabetes: the Diabetes and Aging Study. *Diabetes Care* 2013;36:3535–3542
24. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. *JAMA* 2009;301:1565–1572
25. Schwartz AV, Vittinghoff E, Sellmeyer DE, et al.; Health, Aging, and Body Composition Study. Diabetes-related complications, glycemic control, and falls in older adults. *Diabetes Care* 2008;31:391–396
26. Johnston SS, Conner C, Aagren M, Ruiz K, Bouchard J. Association between hypoglycaemic events and fall-related fractures in Medicare-covered patients with type 2 diabetes. *Diabetes Obes Metab* 2012;14:634–643
27. Green AJ, Fox KM, Grandy S; SHIELD Study Group. Self-reported hypoglycemia and impact on quality of life and depression among adults with type 2 diabetes mellitus. *Diabetes Res Clin Pract* 2012;96:313–318
28. Lee AK, Warren B, Lee CJ, et al. The association of severe hypoglycemia with incident cardiovascular events and mortality in adults with type 2 diabetes. *Diabetes Care* 2018;41:104–111
29. Action to Control Cardiovascular Risk in Diabetes Study Group; Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545–2559
30. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560–2572
31. Miller ME, Bonds DE, Gerstein HC, et al.; ACCORD Investigators. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. *BMJ* 2010;340:b5444
32. Munshi MN, Slyne C, Segal AR, Saul N, Lyons C, Weinger K. Liberating A1C goals in older adults may not protect against the risk of hypoglycemia. *J Diabetes Complications* 2017;31:1197–1199
33. International Hypoglycaemia Study Group. Glucose concentrations of less than 3.0 mmol/L (54 mg/dL) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2017;40:155–157
34. Agiostratidou G, Anhalt H, Ball D, et al. Standardizing clinically meaningful outcome measures beyond HbA_{1c} 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
35. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the International Consensus on Time in Range. *Diabetes Care* 2019;42:1593–1603
36. Beck RW, Bergenstal RM, Cheng P, et al. The relationships between time in range, hyperglycemia metrics, and HbA_{1c}. *J Diabetes Sci Technol* 2019;13:614–626
37. Vigersky RA, McMahon C. The relationship of hemoglobin A1C to time-in-range in patients with diabetes. *Diabetes Technol Ther* 2019;21:81–85
38. Lu J, Ma X, Zhou J, et al. Association of time in range, as assessed by continuous glucose monitoring, with diabetic retinopathy in type 2 diabetes. *Diabetes Care* 2018;41:2370–2376
39. Guo Q, Zang P, Xu S, et al. Time in range, as a novel metric of glycemic control, is reversely associated with presence of diabetic cardiovascular autonomic neuropathy independent of HbA_{1c} in Chinese type 2 diabetes. *J Diabetes Res* 2020;2020:5817074
40. Beck RW, Bergenstal RM, Riddlesworth TD, et al. Validation of time in range as an outcome measure for diabetes clinical trials. *Diabetes Care* 2019;42:400–405
41. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2020*. *Diabetes Care* 2020;43(Suppl. 1):S98–S110

42. Mathieu C, Dandona P, Phillip M, et al.; DEPICT-1 and DEPICT-2 Investigators. Glucose variables in type 1 diabetes studies with dapagliflozin: pooled analysis of continuous glucose monitoring data from DEPICT-1 and -2. *Diabetes Care* 2019; 42:1081–1087

43. Sofizadeh S, Imberg H, Ólafsdóttir AF, et al. Effect of liraglutide on times in glycaemic ranges as assessed by CGM for type 2 diabetes patients treated with multiple daily insulin injections. *Diabetes Ther* 2019;10:2115–2130

44. Mazze R, Cranston I. *Core Curriculum: Ambulatory Glucose Profile (AGP): Background, Rationale and Applications in Clinical Practice*. Portsmouth, U.K., AGP Clinical Academy (Portsmouth Hospitals, NHST), 2019

45. Johnson ML, Martens TW, Criego AB, Carlson AL, Simonson GD, Bergenstal RM. Utilizing the ambulatory glucose profile to standardize and implement continuous glucose monitoring in clinical practice. *Diabetes Technol Ther* 2019;21(Suppl. 2): S217–S225