

Ambulatory Glucose Profiling

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INTRODUCTION

This article introduces ambulatory glucose profiling, an evolving approach to monitoring blood glucose. The concept of ambulatory monitoring of glucose data is analogous to ambulatory monitoring of heart rate and rhythm using Holter monitoring or ambulatory monitoring of blood pressure to determine when and what changes to prescribed therapy are necessary. A benefit of ambulatory glucose profiling is that it aggregates large amounts of glucose monitoring data so that variations in blood glucose can be easily identified. The scope of this article is limited and does not include discussion of how integrating ambulatory glucose profiling can be integrated into clinical practice.

Current measures of blood glucose

Diabetes management is essentially a balancing act between maintenance of good glycemic control to reduce the risk of complications, particularly end organ damage and avoidance of severe hypoglycemia.¹ In most patients with diabetes mellitus, however, glycemic control remains suboptimal despite pharmacological advances and technological advances in insulin delivery devices and glucose monitoring.^{2,3} A major factor in poor glycemic control is lack of adherence to prescribed therapeutic agents, most especially insulin, due in part to fear of hypoglycemia.^{2,4-6}

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DISCLOSURES

Dr. Wright discloses that he is on the advisory board and speakers' bureaus for Abbott Diabetes Care Inc.; Boehringer Ingelheim GmbH; and Eli Lilly and Company. He is on the advisory board for AstraZeneca and Voluntas and does contracted research for Abbott Diabetes Care Inc.

Dr. Manivannan discloses that she has no real or apparent conflicts of interest to report.

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To further complicate matters, there is growing evidence that glycemic variability—fluctuations in the blood glucose level—may contribute to the development and progression of micro- and macrovascular disease in individuals with diabetes, including an association with increased carotid intima media thickening.^{7,8} In the Diabetes Control and Complications Trial, risk of retinopathy progression was significantly greater among conventionally treated vs intensively treated patients, despite comparable glycated hemoglobin A1c (HbA1c)—a finding potentially due to the greater frequency and magnitude of glycemic excursions in conventionally treated patients.⁹ It is thought that glycemic variability causes an overproduction of potentially harmful reactive oxygen species and increased oxidative stress resulting in worsened endothelial function and damaged mitochondria and genomic DNA.^{10,11} Evidence also indicates that glycemic variability is a strong predictor of hypoglycemia, correlates with poor glycemic control, and is predictive of patient satisfaction with an intensive insulin regimen.^{2,12,13} These observations make a compelling argument for glycemic variability as an important measure of glycemic control, and its minimization as an important treatment goal.

HbA1c is considered the gold standard indicator of glycemic control in diabetes management due to its demonstrated correlation with the incidence of micro- and macrovascular complications.¹⁴ However, HbA1c reflects mean blood glucose over 8 to 12 weeks, and cannot characterize diurnal glucose patterns which are essential for safe and effective adjustment of glucose-lowering therapy and the avoidance of glucose variability—most notably, extremes of hypo- and hyperglycemia.^{14,15} For decades, self-monitoring of blood glucose (SMBG) has been the standard measure of glycemic control to guide day-to-day adjustment of therapy. Limitations of SMBG include underreporting (omission of undesirable values), over-reporting (addition of values within target), imprecise reporting, lack of overnight glucose readings, and its episodic nature, all of which result in missed significant hypo- and hyperglycemic events.¹

The advent of continuous glucose monitoring (CGM) allows for the collection of continuous glucose data via a sensor (<5 mm in diameter) placed beneath the skin on the abdomen or arm that takes a reading at set intervals (eg, every 1 to 5 minutes) and can be used for 3 to 7 days at a time.¹⁶ CGM can provide real-time feedback on current glucose levels as well as

retrospective data that provides a more accurate view of glucose patterns over a given time period compared with SMBG.¹ A number of studies, including 2 meta-analyses, have demonstrated the efficacy of CGM in improving glycemic control (including reduced HbA1c) and reducing hypoglycemia.¹⁷⁻²⁰

Despite its benefits, CGM is currently used in diabetes management in only a small percentage of patients with type 1 diabetes (3% among young patients with T1D [≤ 25 years old], and 14% among 26 to 49 year old patients with T1D) and a negligible number with type 2 diabetes.³ While underutilization may be partially attributed to limited reimbursement and patients' perceptions regarding the complexity and inconvenience of CGM, barriers to clinicians' incorporating CGM into their practice are another key factor.¹⁶ Chief among these is the daunting time investment required to become proficient at managing and interpreting the CGM data.¹⁶ There are currently 3 commercial CGM device manufacturers, each requiring its own proprietary software to download and analyze CGM data and create reports, with a myriad of reporting options and no standardization among them regarding report output.¹⁶

Ambulatory glucose profiling

Given the demonstrated benefits of CGM, there is a need for standardization of blood glucose data analysis and presentation in a straightforward and intuitive manner in order to convert the data derived from CGM into actionable information.^{2,14} This process can be accomplished with the ambulatory glucose profile (AGP). The AGP is produced by a data-analysis software program that aggregates CGM data from several days or weeks to statistically and visually characterize glycemic exposure, variability, stability, and time in target range (TIR), thus enabling clinicians and patients to discern patterns of glycemic variation and unrecognized hypoglycemia and make pharmacologic and lifestyle adjustments accordingly (FIGURE 1).^{2,21}

The AGP operates on the principle that in the management of diabetes, more glucose data is better than less when it is presented in a format that can be easily and readily actionable as it provides a more accurate picture about what and where therapy should be adjusted. The AGP program, developed by Mazze et al, in collaboration with the International Diabetes Center in Minneapolis, Minnesota, is a non-proprietary open-source program licensed to device manufacturers for inclusion in their software packages that can read data from any CGM device, regardless of the manufacturer, as well as SMBG monitor downloads.^{1,22} It is recommended that 14 days of CGM data be collected for an accurate, comprehensive analysis of key glucose metrics by AGP.²

The AGP provides unique insights into several areas regarding diabetes pathophysiology and management that

are not available with HbA1c: (1) the glucose perturbations that underlie the diagnosis of diabetes; (2) the underlying dysglycemia as a basis for selection and/or initiation of targeted therapy; and (3) whether current therapy is efficacious and, if not, what therapeutic or behavioral approach would likely provide better control. Consequently, AGP provides a better basis than HbA1c for decision-making regarding the dosage and timing of therapies in individual patients. AGP has been used in clinical trials in conjunction with CGM to characterize the impact of medications on the diurnal glucose profile.²³⁻²⁵ In clinical practice in the United States, AGP is being used in some centers to assist in glycemic control.

An important component of AGP is the standardization of clinical terms and key metrics that was developed with input from an expert panel of US diabetes specialists.^{2,14} These terms and metrics include:²

1. Default blood glucose target range: 70-180 mg/dL
2. TIR (expressed as percentage of readings in range and hours per day in range)
3. Glucose exposure (expressed as mean glucose of all readings, and estimated HbA1c based on average glucose and area under the median curve)
4. Glycemic variability (expressed as standard deviation [SD], coefficient of variation, and interquartile range [IQR])
5. Hypoglycemia: <70 mg/dL, <60 mg/dL, and <50 mg/dL corresponding to low, very low, or dangerously low glucose levels, respectively
6. Hyperglycemia: >180 mg/dL, >250 mg/dL, and >400 mg/dL corresponding to high, very high, or dangerously high glucose levels, respectively
7. Estimated HbA1c is based on the mean glucose for the period under investigation.*

*Since the formula for the estimated HbA1c uses all of the captured glucose values, when subjects have a significant number of glucose values in the hypoglycemic range, the estimated HbA1c will be lower than the measured laboratory HbA1c value.

The default page of the software program is the "dashboard," which presents the most relevant graphical and statistical information to facilitate rapid assessment of the patient's glycemic condition so that the provider can make timely clinical decisions. The patient can view the dashboard simultaneously with the provider, when possible, so that the patient can provide relevant insights and feedback.² The dashboard is composed of 3 parts: (1) statistical summary, (2) visual display, and (3) daily views. The statistical summary includes *glucose exposure* (average glucose and estimated HbA1c based on collected data), *glucose variability* (total SD and IQR of collected data), *glucose ranges* (percentages of values in target range; low, very low, and dangerously low; and high, very high, and

FIGURE 1A Daily ambulatory glucose profile reports over a 6-day period

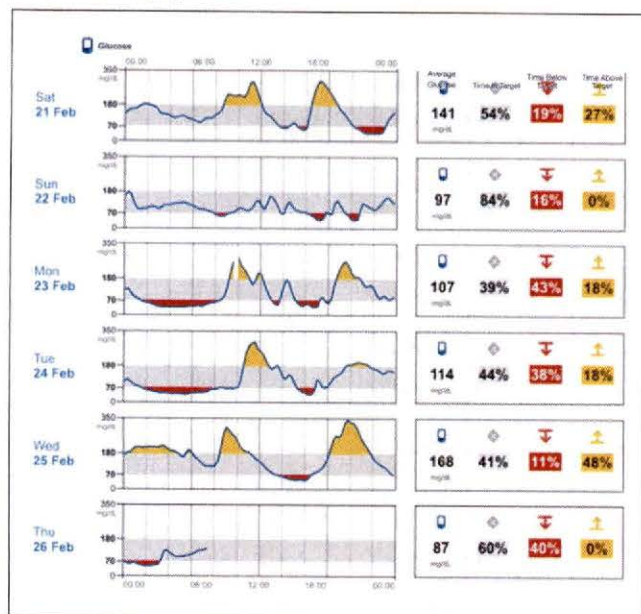


FIGURE 1B Daily patterns with ambulatory glucose profile over 14 days

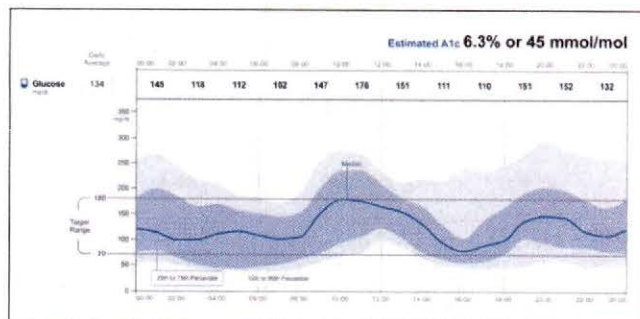


Figure 1a and 1b. The ambulatory glucose profile (AGP) operates on the principle that in the management of diabetes, more glucose data is better than less when it is presented in a format that can be easily and readily actionable. The AGP aggregates glucose data over multiple days to help the patient and providers discern patterns of glycemic variation and unrecognized hypoglycemia. The AGP can take data from several sources to include SMBG monitor downloads to CGM glucose data.

Figure 1a: Daily AGP reports over a 6-day period.

Figure 1b: AGP report that aggregates 14 days of daily AGP reports over a 24-hour period displayed by time to show the spread of glucose values within each time interval. The dark blue line is the median curve (50th percentile) and shows the median glucose value for each time point. The darker blue shaded area represents the interquartile range (IQR). The light blue shaded area represents the outlier values (lowest and highest 10%).

Images courtesy of Dr. Roger Mazze.

dangerously high ranges), and *data sufficiency* (average number of tests per day upon which the data were generated).² An expanded statistical view can be accessed with one click that provides more detailed data regarding these variables.

The visual display section of the AGP dashboard presents a modal day (standard or average day) that is derived by collapsing and plotting according to time (without regard to date) all data collected over multiple days as if they occurred over 24 hours. This is displayed as smoothed curves representing the median (50th), 25th to 75th frequency percentile, and 10th to 90th frequency percentile (**FIGURE 1B**). The median curve is a representation of glucose stability, while the 25th to 75th percentile curve defines the IQR, representing glucose variability, and the 10th to 90th percentile curve tracks glucose excursions.¹⁴ One can easily see the times of day when glucose is most consistently high or low, when the greatest variability occurs, and the magnitude of that variability. For example, the 10th to 90th percentile curve crossing 70 mg/dL or lower at a given time of day indicates a moderate risk of hypoglycemia at that time since 10% of values fall in that range, while the 25th to 75th percentile curve crossing that threshold indicates a greater risk since 25% of values fall into the hypoglycemia range at that time.²

The daily view section of the AGP dashboard consists of a calendar of thumbnail AGPs (target range and median line) of the 24-hour pattern for each day included in the overall profile. This simplifies comparison of patterns on specific days (eg, weekday vs weekend) and facilitates conversations with patients to discern circumstances that might be contributing to glucose variability or excursions.²

Obviously, information about the patient's treatment regimen, adherence, and food intake must be considered in conjunction with the AGP. Currently, the clinician can add such information on the AGP modal day graphic at a clinic visit.²

The AGP provides insight into glycemic variability and hypo- and hyperglycemic excursions that are not possible based solely on HbA1c. In **FIGURES 2A** and **2B**, two subjects have similar HbA1c values (7.4% and 7.8%), but very different daily glycemic patterns. In fact, the patient with the HbA1c of 7.4% has poorer glycemic control in terms of markedly greater blood glucose variability throughout the day, instances of hypoglycemia midday, with several glucose excursions well above 250 mg/dL. The patient with the HbA1c of 7.8% has much less glycemic variability, fewer hyperglycemic excursions above 250 mg/dL, and no instances of hypoglycemia.

CONCLUSION

Glycemic variability is increasingly recognized as an important measure of glycemic control, and its minimization an important treatment goal. CGM provides a comprehensive

FIGURE 2A Daily patterns with ambulatory glucose profile over 9 days

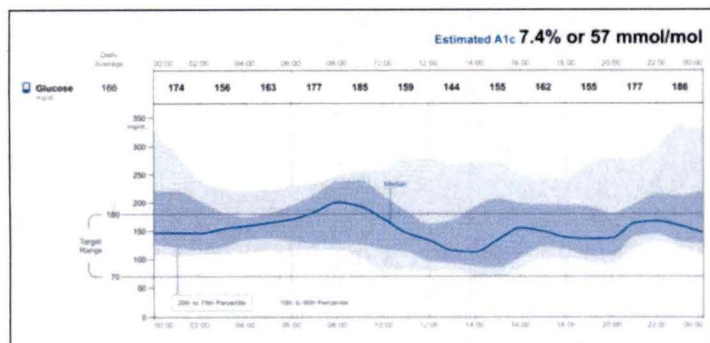


FIGURE 2B Daily patterns with ambulatory glucose profile over 15 days

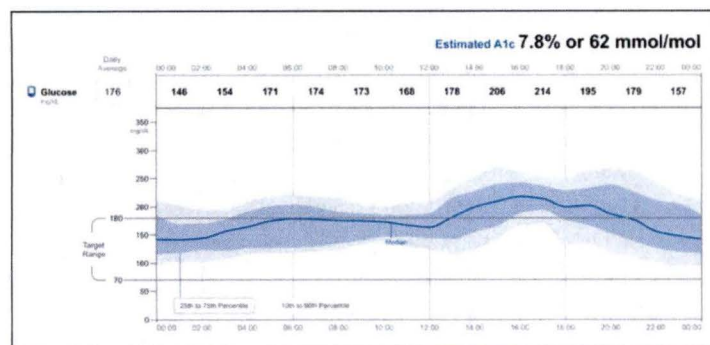


Figure 2a and b. Two patients with similar HbA1c values, but very different daily glycemic patterns.

Figure 2a: Patient with a slightly lower HbA1c has poorer glycemic control in terms of markedly greater blood glucose variability throughout the day, instances of hypoglycemia midday, and several glucose excursions well above 250 mg/dL throughout the day.

Figure 2b: The patient has a slightly higher HbA1c, but much less glycemic variability, fewer hyperglycemic excursions above 250 mg/dL, and no instances of hypoglycemia.

Images courtesy of Dr. Roger Mazze.

view of a patient's glucose levels. However, the amount of data generated can become unmanageable, and there is no standardization among the 3 CGM manufacturers regarding software or report output. Ambulatory glucose profile (AGP) is a data-analysis software program that facilitates the aggregation of CGM data into actionable information by statistically and visually characterizing glycemic exposure, variability, stability, and time in target range. This allows easier discernment of glycemic patterns to inform decisions regarding pharmacologic and lifestyle management. ●

REFERENCES

- Mazze R, Akkerman B, Mettner J. An overview of continuous glucose monitoring and the ambulatory glucose profile. *Minn Med*. 2011;94(8):40-44.
- Bergental 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. *J Diabetes Sci Technol*. 2013;7(2):562-578.
- Beck RW, Tamborlane WV, Bergental RM, Miller KM, DuBose SN, Hall CA. The T1D Exchange clinic registry. *J Clin Endocrinol Metab*. 2012;97(12):4383-4389.
- Morris AD, Boyle DI, McMahon AD, Greene SA, MacDonald TM, Newton RW. Adherence to insulin treatment, glycaemic control, and ketoacidosis in insulin-dependent diabetes mellitus. The DARTS/MEMO Collaboration. *Diabetes Audit and Research in Tayside Scotland. Medicines Monitoring Unit. Lancet*. 1997;350(9090):1505-1510.
- Di Battista AM, Hart TA, Greco L, Glozier J. Type 1 diabetes among adolescents: reduced diabetes self-care caused by social fear and fear of hypoglycemia. *Diabetes Educ*. 2009;35(3):465-475.
- Wild D, von MR, Brohan E, Christensen T, Clauson P, Gonder-Frederick L. A critical review of the literature on fear of hypoglycemia in diabetes: Implications for diabetes management and patient education. *Patient Educ Couns*. 2007;68(1):10-15.
- Esposito K, Ciotola M, Carleo D, et al. Post-meal glucose peaks at home associate with carotid intima-media thickness in type 2 diabetes. *J Clin Endocrinol Metab*. 2008;93(4):1345-1350.
- Monnier L, Colette C, Leiter L, et al. The effect of glucose variability on the risk of microvascular complications in type 1 diabetes. *Diabetes Care*. 2007;30(1):185-186.
- Hirsch IB, Brownlee M. Should minimal blood glucose variability become the gold standard of glycemic control? *J Diabetes Complications*. 2005;19(3):178-181.
- Monnier L, Mas E, Ginnet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA*. 2006;295(14):1681-1687.
- Ceriello A, Esposito K, Piconi L, et al. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. *Diabetes*. 2008;57(5):1349-1354.
- Monnier L, Wojtuszczyk A, Colette C, Owens D. The contribution of glucose variability to asymptomatic hypoglycemia in persons with type 2 diabetes. *Diabetes Technol Ther*. 2011;13(8):813-818.
- Testa MA, Gill J, Su M, Turner RR, Blonde L, Simonson DC. Comparative effectiveness of basal-bolus versus premix analog insulin on glycemic variability and patient-centered outcomes during insulin intensification in type 1 and type 2 diabetes: a randomized, controlled, crossover trial. *J Clin Endocrinol Metab*. 2012;97(10):3504-3514.
- Matthaei S. Assessing the value of the Ambulatory Glucose Profile in clinical practice. *Br J Diabetes Vasc Dis*. 2014;14(4):148-152.
- Kay D. Approaches to display of multiple-point glucose profiles: A UK patient's perspective. *J Diabetes Sci Technol*. 2014;8(6):1233-1238.
- Bhude M, Grey JM, Moser EG, Garg SK. A primary care perspective on the use of continuous glucose monitoring in clinical practice. *Diabetes Technol Ther*. 2013;15(7):533-537.
- Tamborlane WV, Beck RW, Bode BW, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med*. 2008;359(14):1464-1476.
- Anon. Effectiveness of continuous glucose monitoring in a clinical care environment: evidence from the Juvenile Diabetes Research Foundation continuous glucose monitoring (JDRF-CGM) trial. *Diabetes Care*. 2010;33(1):17-22.
- Pickup JC, Freeman SC, Sutton AJ. Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. *BMJ*. 2011;343:d3805.
- Yeh HC, Brown TT, Maruthur N, et al. Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. *Ann Intern Med*. 2012;157(5):336-347.
- Mazze RS, Strock E, Wesley D, et al. Characterizing glucose exposure for individuals with normal glucose tolerance using continuous glucose monitoring and ambulatory glucose profile analysis. *Diabetes Technol Ther*. 2008;10(3):149-159.
- 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(1):111-117.
- Mazze R, Strock E, Morgan B, Wesley D, Bergental R, Cuddihy R. Diurnal glucose patterns of exenatide once weekly: a 1-year study using continuous glucose monitoring with ambulatory glucose profile analysis. *Endocr Pract*. 2009;15(4):326-334.
- Mazze R, Strock E, Cuddihy R, Morgan B. O-0544 Exenatide once-weekly versus twice-daily: comparison of diurnal and postprandial glucose patterns using continuous glucose monitoring and ambulatory glucose profile analysis. *Can J Diabetes*. 2009;33(3):210-211.
- Mazze RS, Strock ES, Monk AM, Murphy MM, Xi M, Bergental RM. Diurnal glucose profiles using continuous glucose monitoring to identify the glucose-lowering characteristics of colesevelam HCl (Welchol). *Endocr Pract*. 2013;19(2):275-283.
- Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ. Translating the A1C assay into estimated average glucose values. *Diabetes Care*. 2008;31(8):1473-1478.

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