REVIEW ARTICLE

Real Time Flash Glucose Monitoring: Now a Reality in India

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Abstract

Tight glycemic control has been recognised as the cornerstone of modern diabetes management. Until recently, glycated hemoglobin (HbA1c) was the only reliable tool for measuring glycemic control, but it is not an ideal metric as it is retrospective, unable to pick up hypo- and hyperglycemic excursions and prone to interference by conditions such as anemia and hemoglobinopathies. The advent of continuous glucose monitoring systems is a giant leap in diabetes management as it enables visualisation of glucose trends over periods of time, helping in identification of hypo- and hypoglycemic events and enabling appropriate treatment decisions to be made. The recent launch of the real-time patient CGM in India is a further step in the right direction as it will empower patients to take control of their diabetes by providing them information on their glucose levels and trends in real time.

Tight glycemic control, aiming for blood glucose levels as close to normal non-diabetic levels as possible, has been shown to reduce the risk of both micro- and macro-vascular complications of diabetes.[1,2] For nearly 50 years since the concept of tight glycemic control was first introduced by Joslin, its achievement remained elusive, primarily due to the absence of a convenient and reliable marker of long-term glycemia. This deficiency was overcome, to a large extent, by the advent of glycated hemoglobin (HbA1c) testing, and maintaining HbA1c at target levels is now part of all established guidelines for diabetes care.[3]

However, the use of HbA1c as a tool to measure glycemic control is not without its disadvantages, some of which are listed below.[4]

1. HbA1c represents the average glycemia over the preceding 2 to 3 months and does not provide information on hypo- and hyperglycemic excursions.

2. HbA1c fails to identify the magnitude and frequency of intra- and inter-day glucose variation

3. The relationship between HbA1c and average glycemia may not be exactly the same in all individuals, such that certain individuals demonstrate an inappropriately high or low HbA1c for their degree of glycemia.

4. HbA1c can be affected by several non-glycemic factors such as altered RBC lifespan, hemoglobinopathies, renal insufficiency and (non-diabetes) medication use.

Therefore, relying solely on the HbA1c to assess an individual's glycemic control does not provide a comprehensive picture of the clinical situation, and may also lead to erroneous treatment decisions. This realization has led to the development of alternative methods of assessing glycemic control that can supplement the HbA1c. The most widely used among these is self-monitoring of blood glucose (SMBG). SMBG is relatively easy to perform, but has the disadvantage that it is operator (patient)-dependent, often leading to data not being available for time periods of interest to the physician to adjust medicine doses. It is also difficult to draw inferences about glycemic trends from the (often disjointed) data generated from SMBG. In other words, the SMBG provides 'Snapshots' of glucose levels at the times when the patient chooses to test providing no idea about the time in between.

Continuous glucose monitoring (CGM)

CGM is a robust technique for assessing the day to day fluctuations and medium- term glycemic trends in patients with diabetes. One can therefore compare the SMBG to 'still photography' and CGM to a 'video'. (Figure 1A and 1B).

CGMS has been in clinical use for more than 20 years now. The traditional

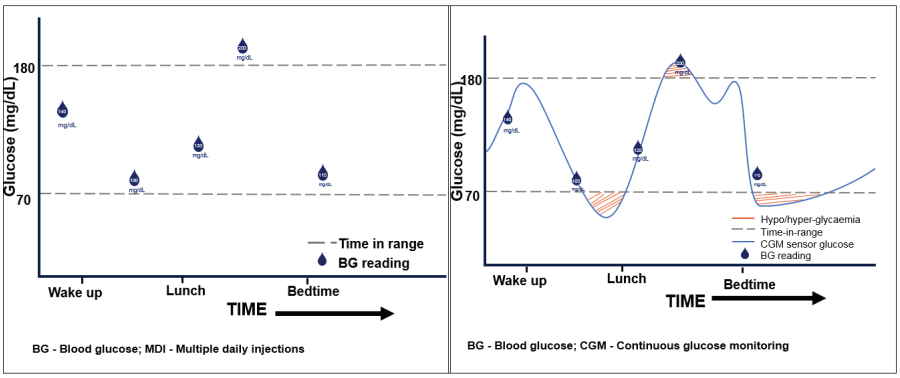

Fig. 1: (A) SMBG measurements do not show trends in glucose; (B) CGM/FGM shows trends of glucose

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Received: ; Accepted:

Table 1: Differences between 'Retrospective' and 'Real Time' flash glucose monitoring systems

	Retrospective flash glucose monitoring	Real time flash glucose monitoring
Type of device	Personal use	Professional use
Sensor wear duration	Up to 14 days	Up to 14 days
Real-time readings	No (Retrospective)	Yes, with a scan of the sensor
How to get glucose readings?	The sensor needs to be brought to the clinic for reading	Patients can scan the sensor by themselves at any time and get real time readings
Fingerstick calibration	Not needed	Not needed
On-the-body equipment	Sensor applied by Health Care Professional (HCP) to the back of the patient's arm; worn for up to 14 days	Sensor applied by patient to the back of his/her own arm; worn for up to 14 days
Reader	• HCP owned and stays in the office/ clinic • One reader can be used for multiple patient sensors	• Patient owned • Patient scans for real-time readings • 1 reader is paired with 1 sensor at a time

CGM systems suffered from various drawbacks such as short duration of recording, requirement for fingerstick calibration, cumbersome sensors and high cost. The advent of flash glucose monitoring (FGM) devices over the last 5 years has revolutionized the field of diabetes monitoring worldwide. Two variants of this system were launched- one meant for patient use, which is a real time FGM and the other meant for use by healthcare professionals. In India, the professional model was made available in 2015. In contrast, in many other regions such as Europe and UK, the patient model was introduced first. Table 1 lists the differences between the professional and patient FGM system.

Both these systems consist of a sensor which is inserted subcutaneously (usually over the upper arm) and a reader that collects data from the sensor when placed close to the sensor ("intermittent scanning"). Both these systems offer considerable advantages when compared to the earlier (non-flash-based) systems. The sensors for both these systems work for a period of 14 days, as compared to 7 days for the older systems. They are factory-calibrated, and hence there is no need for calibration with fingerstick glucose values. The sensor is unobtrusive and its insertion is virtually painless. The system is also less expensive as compared to the earlier traditional CGM systems. Indeed, if one takes into account the number of times the glucose can be tested, it works out to be cost effective. It is also much less cumbersome and practically painless compared to SMBG.

These systems provide their reports in the form of an ambulatory glucose profile (AGP). The proprietary AGP software collapses all CGM data from several days or weeks into a single 24-h period. This helps in providing insights into the glycemic trends for the preceding 2 weeks, which can then be used to predict the patterns for the next 2 to 3 months with a reasonable degree of confidence. The software also calculates such variables as the glucose management indicator (GMI), time in-, above and below range and glycemic variability. This is of immense help to clinicians in adjusting therapies, and in assessing the effects of such adjustments. In view of these advantages, it is probably not surprising that the flash glucose monitoring systems have become popular in India and are widely accepted by clinicians. Consensus Guidelines have also been published on the use of CGM in India.[5]

Recently, an International Panel of experts convened by the Advanced Technologies & Treatments for Diabetes (ATTD) Congress, published guidelines for the reporting of CGM metrics.[6] As per these guidelines, the most important metric derived from CGM is the **"time-in-range"** (TIR). TIR is defined as the proportion of time (usually expressed as a percentage) that an individual spends with his/her blood glucose levels within a prespecified target range (usually defined as 70 to 180 mg/dl). TIR is rapidly emerging as an important complement to HbA1c as a measure of glycemic control and may even replace HbA1c in the future. A recent study from India demonstrated close alignment with TIR in accordance with the International Consensus on TIR for A1c between 7 and 9 %.[7] Higher TIR has been shown to be associated with lower odds of developing severe retinopathy, as well as lower risk of cardiovascular disease and all-cause mortality.[8,9] Table 2 shows the differences between HbA1c and TIR.[4,10] While it is possible to calculate TIR from SMBG data, its accurate measurement requires the use of CGM and flash glucose monitoring systems.

Table 2: Differences between HbA1c vs. TIR[4,10]

Glycated hemoglobin (HbA_{1c})	Time in Range (TIR)
Retrospective measure of average glycemia	Evaluates continuous glucose level
Provides data on control of diabetes over preceding 3 months period	Gives data on 24 hour glycemic excursions over periods ranging from 3 – 14 days
Does not capture hypo- or hyperglycemic excursions	Captures all glucose levels for the given time frame and identifies time spent within safe range
Immediate effects of therapy changes not recorded	Detects acute effects of therapy changes
Bad correlation to Patient reported outcomes (PROs)	Good correlation to PROs
High susceptibility to interference (method and lab-dependent, anaemia, hemoglobinopathy, etc.)	Low susceptibility to interference
Good correlation to clinical endpoints, many long-term studies	Correlation to endpoints unclear, Very few long-term studies on TIR

In a study from multiple diabetes clinics across India, 2536 individuals who had unsatisfactory control of diabetes (HbA1c >7%) were initiated on the professional FGM system and compared with 2536 age, sex and HbA1c-matched individuals who were not put on FGM, after a period of 6 months.[11] Individuals who were initiated on FGM showed greater reduction in HbA1c levels compared to those who were not, even after adjusting for age, gender, body-mass index, systolic blood pressure, time to follow-up A1c, and medication use.

The patient FGM system is meant for patient use and requires the patient to purchase the reader as well as the sensor. It permits the patient to view the glucose trends and levels in real time. The professional model is meant for use by healthcare professionals for detecting trends and tracking patterns and glucose level excursions above or below the desired range, facilitating therapy adjustments. The patient usually purchases only the sensor, while the reader remains in the physician's office, and can be used to

scan the sensors of multiple patients.

However, the professional model suffers from the disadvantage that even if the patient purchases the reader separately, it does not provide real-time glucose values, necessitating the use of capillary glucose meters for immediate diagnosis of hypo- or hyperglycemic events. The advent of the patient model of FGM in India is therefore a welcome step and will help in making patients active partners in decision-making for management of diabetes.

Several studies from Europe have shown the benefits of FGM in patients with both type 1 and type 2 diabetes. In a multicentre, prospective, non-masked, randomized controlled trial of 328 adults with well-controlled type 1 diabetes from 23 diabetes centres, use of FGM was shown to significantly reduce the time spent in hypoglycemia.[12] In a subsequent open-label randomized controlled study of 224 individuals with insulin-treated type 2 diabetes, use of flash glucose monitoring reduced the incidence of all hypoglycemia by 43% and that of nocturnal hypoglycemia by 58%.[13]

A recent series of three retrospective non-interventional medical record review studies, including patients with type 2 diabetes managed on basal bolus insulin therapy from Austria, Germany and France, showed that use of FGM was associated with significant reductions in HbA1c (ranging from 0.9±1.1% in Germany to 0.8 ±1.1% in France) after 3 to 6 months of device use.[14] HbA1c improvement was observed from sub-group analysis across age, sex, duration of insulin and BMI categories for each country.

The FLARE-NL registry was set up in the Netherlands to assess the effects of use of the FGM system on HbA1c, frequency and severity of hypoglycemia, quality of life, and experienced disease burden over 1 year.[15] In this study of 1365 mostly middle-aged individuals, most of whom had type 1 diabetes, there was a significant reduction in HbA1c over the 1 year of FGM use. Individuals reported fewer episodes of hypoglycemia, less absenteeism from work and scored better on quality of life scores and lower on perceived disease burden scores after FGM use.

The advent of flash glucose monitoring represents a significant advance in diabetes care in India. Patients who use the system are able to obtain a real time glucose reading, a trend indicator and history of glycemic excursions over the preceding 8 hours, each time they scan their sensor. The patient is also able to visualize daily trends, the time in range and hypoglycemic episodes. However, the sheer magnitude of data generated by the system may feel overwhelming to some patients. Patients should therefore be given appropriate education on how best to interpret the data provided by their monitoring system and how to utilize it to make the most appropriate decisions. It is hoped that the HbA1c of our patients in India will further improve after introduction of these devices, which represent a big step forward in personalized or precision diabetes monitoring.

References

1. UKPDS Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38). *BMJ* 1998; 317:703–713.
2. The 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. *New Engl J Med* 1993; 329:977–986.
3. American Diabetes Association. Position Statements. Glycemic Targets: Standards of Medical Care in Diabetes 2020. *Diabetes Care* 2020; 43(Supplement 1): S66-S76.
4. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, Garg S, Heinemann L, Hirsch I, Amiel SA, Beck R, Bosi E, Buckingham B, Cobelli C, Dassau E, Doyle FJ 3rd, Heller S, Hovorka R, Jia W, Jones T, Kordonouri O, Kovatchev B, Kowalski A, Laffel L, Maahs D, Murphy HR, Nørgaard K, Parkin CG, Renard E, Saboo B, Scharf M, Tamborlane WV, Weinzimer SA, Phillip M. International Consensus on Use of Continuous Glucose Monitoring. *Diabetes Care* 2017; 40:1631-1640.
5. Chawla M, Saboo B, Jha S, Bhandari S, Kumar P, Kesavadev J, Munjal YP, Mohan V, Unnikrishnan R, Katswar V, Arun N, Sosale B, Anjana RM, Hasnani D. Consensus and recommendations on continuous glucose monitoring. *J Diabetol* 2019; 10:4-14.
6. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, Bosi E, Buckingham BA, Cefalu WT, Close KL, Cobelli C, Dassau E, DeVries JH, Donaghue KC, Dovc K, Doyle FJ 3rd, Garg S, Grunberger G, Heller S, Heinemann L, Hirsch IB, Hovorka R, Jia W, Kordonouri O, Kovatchev B, Kowalski A, Laffel L, Levine B, Mayorov A, Mathieu C, Murphy HR, Nimri R, Nørgaard K, Parkin CG, Renard E, Rodbard D, Saboo B, Schatz D, Stoner K, Urakami T, Weinzimer SA, Phillip M. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. *Diabetes Care* 2019; 42:1593-1603.
7. Kesavadev J, Shankar A, Warrier R, Krishnan G, Shamsudeen J, Jothydev S. Outlining the Relationship Between Time In Target (TIT) and HbA1c in Asian Indians with Diabetes. *Diabetes Technol Ther* 2020; 22(S1):A131.
8. Lu J, Ma X, Zhou J et al. Assoaication of time-in-range, as assessed by continuous glucose monitoring, with diabetic retinopathy in type 2 diabetes. *Diabetes Care* 2018; 41:2370-2376.
9. Lu J, Wang C, Shen C et al. Time in range in relation to all-cause and cardiovascular mortality in patients with type 2 diabetes: A prospective cohort study. *Diabetes Care* 2020 Oct 23;dc201862. doi:10.2337/dc20-1862. (Online ahead of print)
10. Agiostratidou G, Anhalt H, Ball D, Blonde L, Gourgari E, Harriman KN, Kowalski AJ, Madden P, McAuliffe-Fogarty AH, McElwee-Malloy M, Peters A, Raman S, Reifschneider K, Rubin K, Weinzimer SA. 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.
11. Anjana RM, Kesavadev J, Neeta D, Tiwaskar M, Pradeepa R, Jebarani S, Thangamani S, Sastry NG, Brijendra Kumar S, Ramu M, Gupta PPK, Vignesh J, Chandru S, Kayalvizhi S, Jagdish PS, Uthra SCB, Lovelena M, Jyoti S, Suguna Priya S, Kannan A, Mohan V, Unnikrishnan R. A Multicenter Real-Life Study on the Effect of Flash Glucose Monitoring on Glycemic Control in Patients with Type 1 and Type 2 Diabetes. *Diabetes Technol Ther* 2017; 19:533-540.
12. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. *Lancet* 2016; 388:2254-2263.
13. Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline JP, Rayman G. Use of Flash Glucose-Sensing Technology for 12 months as a Replacement for Blood Glucose Monitoring in Insulin-treated Type 2 Diabetes. *Diabetes Ther* 2017; 8:573-586
14. Kröger J, Fasching P, Hanaire H. Three European Retrospective Real-World Chart Review Studies to Determine the Effectiveness of Flash Glucose Monitoring on HbA1c in Adults with Type 2 Diabetes. *Diabetes Ther* 2020; 11:279-291.
15. Lameijer A, Fokkert MJ, Edens MA, Slingerland RJ, Bilo HJG, van Dijk PR. Determinants of HbA1c reduction with FreeStyle Libre flash glucose monitoring (FLARE-NL 5). *J Clin Transl Endocrinol* 2020; 22:100237.