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Sudhir Tripathi[1], Sushil Jindal[2], Manoj Chawla[3], Arvind Gupta[4], Sujeet Jha[5], Uday Phadke[6], Tejal Lathia[7]

[1]Sir Gangaram Hospital, New Delhi, India
[2]Department of Endocrinology, People's College of Medical Sciences and Research Centre, Bophal, India
[3]Lina Diabetes Care Centre, Andheri West, Mumbai, India
[4]Rajasthan Hospital, Jaipur, India
[5]Max Hospital, Saket, New Delhi, India
[6]Department of Endocrinology and Diabetes, Sahyadri Hospitals, Pune, India
[7]Department of Endocrinology, Apollo Hospitals and Fortis Hospital, Mumbai, India

The Implication of Time-in-Range for the Management of Diabetes in India: A Narrative Review

ABSTRACT

Introduction: In recent times, traditional self-monitoring of blood glucose (SMBG) using fingerstick capillary samples is moving to continuous glucose monitoring (CGM) due to inherent limitations of the traditional methods. CGM displays current glucose level, trends, rate of change, time-in-range (TIR), and glucose variability (GV) over a period of several days. It detects episodes of hyperglycemia and hypoglycemia, which allows immediate response to prevent these episodes. It also allows physicians to provide a personalized glycemic response to the patients.

Materials and methods: Though CGM systems have been available for more than 20 years, their use is quite low. It is challenging for clinicians to invest time in learning and understanding the diverse reports of the various CGM devices. Moreover, there is a lack of consensus on the frequency of TIR measurement. Hence. a review of the literature was performed and existing guidelines from India and abroad were reviewed for a need for CGM and its frequency of measurements in DM patients.

Results: TIR is inversely correlated to the risk of microvascular and macrovascular complications. CGM is recommended by expert clinician consensus and national and international medical organizations. For the patients use of CGMs involves cost. Besides, there is the discomfort and inconvenience of wearing the device. Hence, defining the implications of using CGM in practice is important. According to the 2020 recommendations by the Research Society for the Study of Diabetes in India (RSSDI) — Endocrine Society of India (ESI) and the 2019 recommendations by an expert group of endocrinologists and diabetologists, in the Indian context, CGM could be suggested for patients with Type 2 Diabetes who encounter severe hyperglycemia or hypoglycemia, repeated hypoglycemia, asymptomatic hypoglycemia, nocturnal hypoglycemia, refractory hyperglycemia, or large blood glucose excursions.

Conclusions: The role of CGM to achieve better glycemic control and prevention of complications in T1D and T2D is well established. Significant education and awareness on CGM needs to be provided to physicians as well as patients with high GV and those on insulin therapy. (Clin Diabetol 2022, 11; 3: 192–199)

Keywords: time-in-range, blood glucose, diabetes, nocturnal hypoglycemia, asymptomatic hypoglycemia, refractory hyperglycemia, glucose monitoring, repeated hypoglycemia

Address for correspondence:
Dr. Manoj Chawla
Lina Diabetes Care Centre, Andheri West, Mumbai, India
linadiabetes@gmail.com
9820002333
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Introduction

In the last decade, traditional self-monitoring of blood glucose (SMBG) using fingerstick capillary glucose checks is moving to continuous glucose monitoring (CGM) in type 1 diabetes (T1D) and more recently, type 2 diabetes (T2D). Real-time CGM indicates the current glucose level, glucose trends, and rate of change, which can help in immediate response to prevent acute hypoglycemia and hyperglycemia. The glucose trend data helps analyze glycemic patterns and suggest therapy adjustments and/or lifestyle and behavior changes. HbA1c has long been considered the "gold standard" for evaluating glycemic management. However, it has several limitations. HbA1c only indicates the average glucose over 2–3 months and does not reflect glucose variability or hypoglycemia or the magnitude and frequency of intraday and interday glucose fluctuations [1]. Evidence shows that severe hypoglycemia is linked to excessive morbidity and mortality. Increased glycemic variability (GV) is a strong predictor of hypoglycemia and is correlated with poor glycemic control [2]. Real-time continuous glucose monitoring (rtCGM) and intermittently viewed CGM (iCGM) address many of the limitations of HbA1c testing and SMBG.

Continuous glucose monitoring

Continous glucose monitoring provides information about glucose concentration, direction, and rate of change over a period of several days [3]. The device comprises a transcutaneous probe (sensor) that obtains interstitial fluid glucose readings every 5–15 minutes depending on the model. The sensors can stay in place from several days to 6 months, depending on the model used. The devices provide hourly, daily, and weekly glucose trends and patterns [4]. CGM can be used in real-time by the patient and in a masked "professional" mode intended for retrospective review by a healthcare professional [5].

The evolution of CGM

The first CGM prototypes in the early 1970s had an in-line venous cannula to measure glucose, based on which it calculated the correct insulin and dextrose infusion rate. However, it required constant supervision, was bulky, and involved continuous withdrawing and discarding of venous blood. In the past 2 decades, there has been considerable progress. The first CGM device commercially available in 1999 was worn like a wristwatch and provided glucose measurements every 10 minutes via transdermal extraction of interstitial fluid by reverse iontophoresis. However, they had limitations, including skipped readings, skin irritation[3], and inaccuracy, and its measurement error was more than –20% [5]. Most current CGM devices have subcutaneous sensors to determine the interstitial glucose concentration [3]. Today, overall measurement error has been reduced by twofold (–10%), and accuracy continues to improve. The size, weight, complexity, and cost of CGM sensors/devices have decreased. Simultaneously, the duration of use, specificity, user-friendliness, user interface and displays, data management, and software for data analysis have improved [5]. However, they require frequent calibration by fingerstick tests and cannot be used for more than a few days. Some of the recently developed CGM devices are wireless; their sensors are inserted into the subcutaneous tissue of the abdomen or upper arm [3]. Another development is Flash glucose monitoring (FGM). It is a factory-calibrated device, with an on-body sensor that is worn on the back of the arm for up to 14 days and automatically stores glucose data every 15 minutes [6].

Interpreting the CGM data: Ambulatory Glucose Profile (AGP) Software

The data produced by CGM devices is often unmanageable. Hence, a universal software report, the Ambulatory Glucose Profile (AGP) has been developed. AGP standardizes clinical terms and key metrics and presents glucose data visually, making it easy to interpret [7].

A standardized AGP is a "simplified" single-page document for use in clinical practice. The AGP dashboard presents a summary of the glucose data in three parts: (1) statistical summary, (2) visual display, and (3) daily views. The data includes the average glucose and estimated HbA1c, GV, and percentage of values in the target range (default 70–180 mg/dL), low ranges, very high, and dangerously high ranges. It also displays the Glucose Management Indicator (GMI), which is calculated from the average glucose and estimates the future lab A1c [2] (Fig. 1).

Time-in-Range (TIR)

Time in range refers to the time spent in the target glucose range [1]. TIR has also been recommended as an appropriate endpoint in clinical research to evaluate glycemic control in patients with diabetes [8]. However, this end-point has not been approved by regulatory bodies in the United States and European Union.

International consensus for the use of CGM and TIR

The use of CGM is recommended by expert clinician consensus and national and international medical organizations for individuals with diabetes on intensive

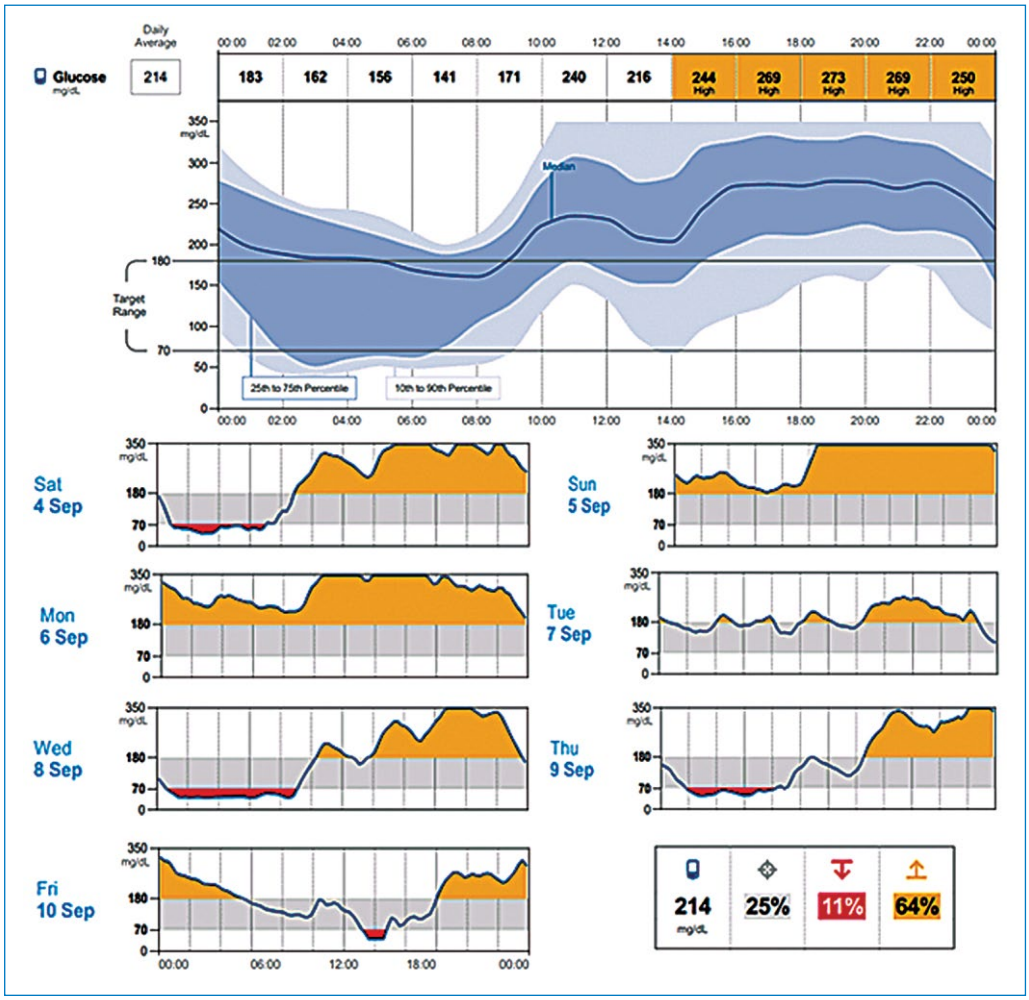


Figure 1 Ambulatory Glucose Profile (AGP): Components at a Glance [11]

insulin therapy and/or those at risk for hypoglycemia [1]. The first expert panel recommended the standardization of CGM reports and metrics in 2012 [2]. Subsequently, several consensus statements have attempted to refine the core CGM metrics [8–10]. However, these were not formally adopted by professional organizations and in clinical practice. In February 2019, the Advanced Technologies and Treatments for Diabetes (ATTD) Congress convened an international panel of experts to arrive at an international consensus on the practical application of CGM metrics and recommend CGM targets for clinical practice. The panel selected 10 metrics that might be most useful in clinical practice as below (Tab. 1).

This report has been endorsed by the American Diabetes Association, American Association of Clinical Endocrinologists, American Association of Diabetes Educators, European Association for the Study of Diabetes, Foundation of European Nurses in Diabetes, International Society for Pediatric and Adolescent Diabetes, Juvenile Diabetes Research Foundation (JDRF), and Pediatric Endocrine Society. The group reached a consensus on glycemic targets and the time that should be spent in each range for individuals with T1D and T2D and for pregnant women with T1D/T2D. (Fig 2) [11].

Challenges ff using CGM

Though CGM systems have been available for more than 20 years, their use is quite low. This is due to several challenges associated with them.

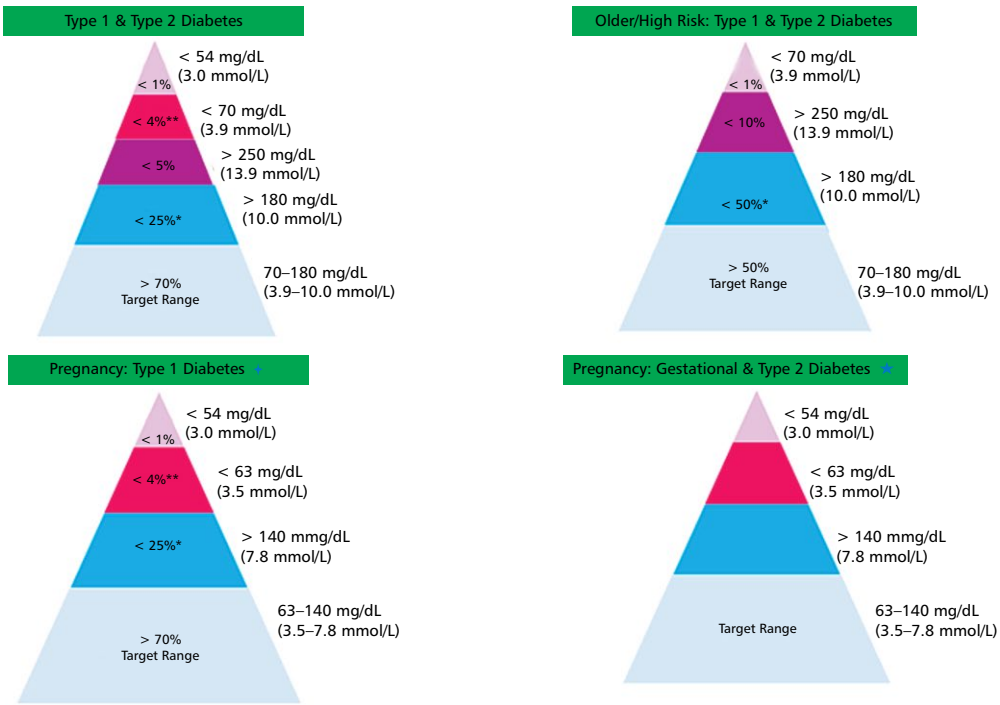
Clinical inertia — resource (physician) challenges

Very few physicians have adopted a systematic approach to interpreting CGM data. This is due to several factors. The first is a lack of standardization. The various CGM devices do not have a standardized method of reporting data; clinicians are unwilling to invest time in learning and understanding the diverse reports [12]. Further, the time involved in downloading

Table 1. Standardized CGM Metrics for Clinical Care: 2019 [11]

Total days for which CGM was worn (recommend 14 days)	
Total duration of time (percentage) for which CGM was active (recommend 70% of data from 14 days)	
Mean blood glucose level	
Glucose management indicator (GMI)	
Glycemic variability (% CV) [recommended target ≤ 36%]	
Time above range (TAR): % of readings and time during which blood glucose level was > 250 mg/dL (>13.9 mmol/L)	Level 2
Time above range (TAR): % of readings and time during which blood glucose level was 181–250 mg/dL (10.1-13.9 mmol/L)	Level 1
Time in range (TIR): % of readings and time during which blood glucose level was 70-180 mg/dL (3.9–10.0 mmol/L)	In range
Time below range (TBR): % of readings and time during which blood glucose level was 54–69 mg/dL (3.0–3.8 mmol/L)	Level 1
Time below range (TBR): % of readings and time during which blood glucose level was < 54 mg/dL (< 3.0 mmol/L)	Level 2
Use of Ambulatory Glucose Profile (AGP) for CGM report	

CGM — continuous glucose monitoring; CV, coefficient of variation



For age < 25 years, if the A1C goal is 7.5%, then set TIR target to approximately 60%. See Clinical Applications of Time in Ranges section in the text for additional information regarding target goal setting in pediatric management).

Percentages of time in ranges are based on limited evidence. More research is needed

Percentages of time in ranges have not been included because there is very limited evidence in this area. More research is needed. Please

*Includes percentage of values > 250 mg/dL (13.9 mmol/L).

**Includes percentage of values < 54 mg/dL (3.0 mmol/L).

Figure 2. CGM-Based Targets for Different Diabetes Populations [11]. CGM — continuous glucose monitoring

and perceiving the complex data consumes time and disrupts the workflow in clinical practice [1]. Other challenges include a lack of reasonable reimbursement for the physician's time and for additional resources required to support CGM (e.g., office staff, computers, printers, internet access, and information technology support services). There is also the risk of a potential medico-legal liability. Moreover, physicians are reluctant to spend time familiarizing themselves with methods serving a minority of patients [5].

Patient-related challenges

Calibration of CGMs using capillary blood glucose meters and reagent strips involves cost, discomfort,

and inconvenience. The false alarms for hyper- and hypoglycemia are disturbing [5]. There are other challenges with the physical experience of wearing devices, including the hassle and discomfort of wearing them, not liking how the devices look on one's body, and issues with insertion, tape, and skin reactions. There is also the nervousness of relying on technology and spending time learning the technology [13, 14].

Cost challenges

Cost is a major barrier. Health plans, insurance companies, and governments in most countries do not cover CGM since they perceive no clear or unique benefit that necessitates reimbursement. The short sensor lifetime adds to the cost for the patient [5]. There is also the cost of regular fingertip blood glucose readings to calibrate the device [15]. Moreover, the CGM technology performance and functionality are rapidly evolving; hence, any device obtained today is likely to be outdated in the near future [5]. In a country like India, assuming that the daily costs for CGM usage are in the range of $5–10 (INR 370 – INR 740) per day, this adds to $3,000 (INR 2,22,635) per year per patient; a very minuscule proportion of the population can afford such a cost.

Lack of clarity about the frequency of CGM and TIR measurement

Though there is clarity of CGM in T1DM, a lack of a standard consensus on CGM and the ideal frequency of CGM in T2DM exists. According to the 2019 ATTD consensus recommendations, 70% use of CGM over the most recent 14 days correlates strongly with 3 months of mean glucose, TIRs, and hyperglycemia metrics. Longer-term CGM data might be necessary in individuals with considerable fluctuations in glycemia (e.g., 4 weeks of data to investigate recurrent hypoglycemia) [11]. The ADA Standards of Medical Care in Diabetes 2020 provides no recommendations about the frequency of CGM measurement [16]. The Endocrine Society Clinical Practice Guideline on diabetes technology recommends rT-CGM devices for adults with T1D having A1C levels above target and willing and able to use these devices on a daily basis (level of evidence 1). Short-term, intermittent rT-CGM use is recommended for adults with T2D (not on prandial insulin) having A1C levels > 7% and willing and able to use the device (level 2 evidence) [17].

Based on the various recommendations by different international associations, the Research Society for the Study of Diabetes in India (RSSDI)- Endocrine Society of India (ESI) Clinical Practice Recommendations for the Management of Type 2 Diabetes Mellitus 2020 suggest that rT-CGMs should preferably be used daily to gain maximal benefit [4].

Relevance of using CGM

Indications for the use of professional CGM in the Indian population

Although CGM-based TIR assessment is useful, access and affordability issues prevent its wide use. According to RSSDI-ESI, the use of professional CGM might help improve glucose control in patients with uncontrolled T2D when average HbA1c values remain above target and in patients on acute and intensive glucose-lowering regimens. In special cases such as pregnant women, children, and adolescents, it might help monitor prandial insulin doses and other dietary decisions. It could be used as a preferred method to monitor blood glucose in critically ill patients. Thus, RSSDI-ESI recommends professional CGM for patients with T2D on treatment under SMBG guidance who encounter severe hypoglycemia, repeated hypoglycemia, asymptomatic hypoglycemia, or nocturnal hypoglycemia, and refractory hyperglycemia, especially when fasting, or large blood glucose excursions [4].

A Diabetes India Task Force of experts in 2019 suggested Indian Clinical Guidelines for CGM, based on the published international guidelines, Indian studies, and their own clinical experiences. They recommended that all T1D patients are candidates for CGM because they are prone to hypoglycemia. The devices must be used on a near-daily basis to achieve and maintain target HbA1c levels. Another group of patients in whom CGM could be recommended in patients with T2D dependent on exogenous insulin, especially if they experience hypoglycemia when trying to maintain their A1C < 7%. CGM in conjunction with intensive insulin regimens can be a useful tool to lower A1C in adults with T1D or T2D with uncontrolled hyperglycemia. It might be a supplement to SMBG in patients with hypoglycemia unawareness or frequent hypoglycemic episodes. Intermittent use of professional CGM might be useful for those with T1D experiencing changes to their diabetes regimen or experiencing nocturnal hypoglycemia/Dawn phenomenon, hypoglycemia unawareness, and postprandial hyperglycemia. In addition, CGM can be used in patients with diabetic gastroparesis and fulminant T1D, and patients with other endocrine and metabolic disorders including insulinoma [15].

An expert group of endocrinologists and diabetologists in India in 2019, suggested the clinical indications for the use of CGM in India for patients on oral antidiabetic drugs (OADs) (Tab. 2) [12].

Moreover, evaluation of CGM metrics can be a big tool to motivate, educate and teach patients with

Table 2. Clinical Indications for AGP in T2D Patients on OADs [12]

- Disparity between FBS/PPBS levels and HbA1c
  - — HbA1c > 7.5%, with FBS/PPBS levels on target
  - — HbA1c on target, with FBS/PPBS levels not on target
- At risk/with hypoglycemia episodes
- Need for patient education
  - — Not adherent to life style modification
  - — Noncompliance to treatment

AGP — ambulatory glucose profile; FBS — fasting blood sugar; HbA1c — glycaated hemoglobin; OAD — oral antidiabetic drug; PPBS — postprandial blood sugar; T2D — type 2 diabetes

diabetes in clinical practice, particularly patients not adherent to medications and lifestyle modifications

Relevance of CGM in preventing micro/macrovascular complications

Recent evidence indicates that TIR is inversely correlated to the risk of developing microvascular and macrovascular complications in patients with diabetes [16–19]. A study evaluated the association of time in range (TIR) of 70–180 mg/dL with the development or progression of retinopathy and development of microalbuminuria using the Diabetes Control and Complications Trial (DCCT) data set in 1440 patients. The hazard rate of development of retinopathy increased by 64% and development of the microalbuminuria increased by 40% for each 10 percentage points lower TIR ($p < 0.001$ for each) [19]. A recent study by Lu et al. [18] demonstrated a significant association between TIR and the prevalence of diabetic retinopathy (DR) in a cohort of 3262 individuals with T2D. Patients with more advanced DR had significantly less TIR and higher measures of GV (all p for trend < 0.01). The association of TIR with diabetic peripheral neuropathy (DPN) was seen in a prospective observational cohort study among 105 patients with T2D. TIR of 70–180 mg/dL (3.9–10.0 mmol/L) was evaluated with CGM worn over two 6-day periods. Less time in range was significantly associated with a greater prevalence of DPN [20]. TIR is also associated with carotid intima-media thickness (CIMT). In a study, data from 2,215 patients with T2D were cross-sectionally analyzed. TIR in the range of 3.9–10.0 mmol/L was evaluated with CGM. Compared with patients with normal CIMT, those with abnormal CIMT had significantly lower TIR ($p < 0.001$). The prevalence of abnormal CIMT progressively decreased across the categories of increasing TIR (p for trend < 0.001) [21]. In the DEVOTE study among 5644 patients with T2D at high risk for cardiovascular events the risk of a major adverse cardiovascular event (MACE) were more by 27% and 31% in those with a dTIR ≤ 70% and ≤ 50% respectively, than in those with a dTIR > 70%.

Implications of using CGM and improving TIR by focusing on insulin therapy

Considering the challenges and the relevance of CGM, it is important to define the implications of using CGM in practice. Questions that need to be addressed include the feasibility of using CGM and measuring TIR in patients with high GV, whether TIR can be derived from SMBG in patients who cannot afford CGM, and whether this data can be used to optimize insulin therapy for glycemic control.

GV or TIR: which is better?

GV is emerging as an important metric for assessing glycemic control in clinical practice. It refers to fluctuations in blood glucose levels and includes postprandial spikes in blood glucose as well as hypoglycemic events. It has been proven that long-term GV is associated with an enhanced risk of micro and macrovascular complications, independent of HbA1c levels [12]. The 2 main parameters indices in evaluating GV are the amplitude of glucose excursions and time spent outside a target range (i.e., time spent in the hypoglycemic or hyperglycemic ranges). However, there is no uniformly accepted standard of measurement (a gold standard) for GV, which is a challenge for its use in clinical practice [23]. TIR, time below range (TBR), and time above range (TAR) should be used together to get the complete picture of GV.

Using SMBG-based dTIR vs. CGM-based TIR

Although there is a consensus about using TIR to assess the control and risk of complications associated with hypo and hyperglycemia, the equivalence between TIRs assessed by different glucose modalities has not been clearly demonstrated. Some studies have shown a high degree of concordance between CGM-based TIR and calculated TIR from SMBG. However, the %TIR from rTCGM and derived TIR (dTIR) from various SMBGs demonstrated clinically and statistically significant differences in the data collected simultaneously in a large cohort with T1D over 26 weeks. These differences were most marked at night.[24] Hence, %TIR targets might vary by monitoring choice and methods of calculation, and harmonization of TIR standards might be challenging.

Opportunities to improve TIR — focus on insulin therapy

Continous glucose monitoring enables more frequent monitoring and can detect more episodes of hyperglycemia and hypoglycemia. This makes it feasible to safely achieve glycemic targets in patients

on insulin. It also facilitates the selection of the most effective insulin therapy and titrates the dose based on CGM metrics. Many recent studies comparing different types of insulins have used CGM for evaluation and shown its utility in achieving target TIRs. The SWITCH PRO NCT03687827 study compared the effect of degludec versus glargine U100 on glycemic control in a randomized, crossover, multicenter trial among insulin-treated adults with T2D having ≥ 1 risk factor for hypoglycemia. The mean TIR was 72.1% for degludec vs. 70.7% for glargine U100 (p = 0.03), a difference of 20.6 min/d). Overall time in tight glycemic range was 21.9 min/d higher with degludec. Degludec also reduced nocturnal TBR (< 3.9 mmol/L) by 12.7 min/night compared with glargine U100, and significantly fewer nocturnal hypoglycemic episodes were observed. More patients on degludec achieved a clinically significant difference (≥ 5%) in TIR [25].

Bergenstal et al. [26] compared glucose control in participants with T1D receiving insulin glargine 300 U/mL (Gla-300) or glargine 100 U/mL (Gla-100) in the morning or evening, in combination with mealtime insulin. Mean 24-h glucose curves for the Gla-300 group were smoother (lower glycemic excursions), irrespective of morning or evening injection. Percentage TIR was comparable between the groups. Reduced nocturnal hypoglycemia was observed with Gla-300 versus Gla-100. Yamabe et al. [27] compared the efficacy and safety of insulin glargine 300 U/mL (Gla300) and insulin degludec U100 (Deg) using FGM.[27] A total of 24 Japanese patients with T2D were randomized to receive once-daily Gla300 (n = 12) or Deg (n = 12) in the morning. Time spent < 70 mg/dL, 70–179 mg/dL, or ≥ 180 mg/dL was not significantly different between the groups. The Faster aspart - GoBolus study by Danne et al. [28] investigated the real-world effectiveness of faster aspart in patients with T1D using iCGM) systems. Adults with T1D (HbA1c, 7.5–9.5%) receiving multiple daily injections of insulin and using iscCGM within local healthcare settings for >6 months were switched to faster aspart at study start. The exploratory endpoint was a change in iscCGM metrics from baseline to week 24. Switching to faster aspart improved HbA1c, increased TIR, and decreased time in hyperglycemia without affecting time in hypoglycemia. For patients with adequate iscCGM data (n = 92), TIR 3.9–10.0 mmol/L increased from 46.9% to 50.1% (p = 0.01), corresponding to an increase of 46.1 min/day.

Malecki et al. [29] used CGM to evaluate treatment with ultra-rapid lispro (URLi) or lispro used in combination with insulin glargine or degludec in adults with T1D. URLi (n = 97) or lispro (n = 99) given 0–2 min before the start of the meal (mealtime) was compared with URLi (n = 73) given 20 min after the meal (postmeal URLi). It was seen that mealtime URLi increased the TIR (71–180 mg/dL) compared to mealtime lispro. Postmeal URLi showed similar postprandial glucose control as mealtime lispro, but less optimal control compared to mealtime URLi. CGM monitoring thus detected increases in time spent in hyperglycemia or decreases in time spent in hypoglycemia in the postmeal URLi arm, which was not possible with SMBG.

This evidence clearly highlights the role important role of CGM in preventing GV and increasing the TIR in patients on insulin.

Conclusions

The benefits of CGM in T1D and T2D for better glycemic control and prevention of complications cannot be denied. However, despite 20 years since their introduction, the use remains low due to various challenges, of which, the cost is perhaps the most significant challenge in a country like India. Nevertheless, significant education and awareness need to be provided to physicians as well as patients to emphasize their use in patients with high GV and those on insulin therapy.

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Conflicts of interest

None declared.

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