Review Article

Positioning "Time-in-Range" in the Treatment of Diabetes in India

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Abstract

Recent increases in the usage of continuous glucose monitoring technology have provided people living with diabetes and health-care professionals with access to a variety of novel glucose control indicators. Some of these indicators are valuable for research, while others are useful clinically. Time-in-range (TIR) is a metric that denotes the proportion of time per day that a person's glucose level is within a specified goal range. There is evidence relating TIR to risk of complications and it is becoming an excepted endpoint in clinical trials. There is an inverse relationship between TIR and glycated hemoglobin. In addition, the duration and severity of time below range and time above range are also discussed. This paper summarizes recent guidelines regarding the "TIR" goals for different individuals with different types of diabetes. As is always the case, glycemic objectives should be tailored to the individual. Finally, this article discusses the tool of TIR's positioning in India and the specific populations/patient profiles that will benefit from the intervention.

Keywords: Continuous glucose monitoring, glycemic variability, hemoglobin A1c, time above range, time below range, time-in-range, type 1 diabetes mellitus, type 2 diabetes mellitus

Introduction

The prevalence of diabetes mellitus (DM), is rising rapidly and is now reaching pandemic proportions.[1] According to the International Diabetes Federation Atlas 2021, 10th Edition, there are 74.2 million people having diabetes in India and this number will increase to 124.9 million in India by 2045, by which time 783 million people will have diabetes worldwide.[2]

Studies conducted in India have revealed a secular trend in increase in the prevalence of diabetes.[3] Recent studies report a diabetes prevalence of up to 25% in some urban areas and up to 16% in some rural areas.[4,5]

For proper management of diabetes, monitoring of glucose levels is extremely important. Self-monitoring of blood glucose (SMBG) is the primary method for assessing and managing glycemic control. SMBG delivers quick results via finger-stick measurements.[6] SMBG glucose readings can be used to track the glycemic effects of diabetes medicines, diet, and exercise.[7] This method is however limited due to physical pain, inconvenience, inaccuracy of results, especially in capillary blood glucose readings, and the cumbersome data collection. Furthermore, because SMBG is a single point-in-time reading and is user-dependent, highs and lows in glucose may be missed at many times, whereas continuous glucose monitoring (CGM) detects glucose 24 × 7, regardless of user intervention.[7] Secondly, capillary blood glucose readings provide considerably less information than continuous glucose sensors, which sample every 5–10 min.[8]

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Inadequate diabetes control results in morbidity due to the chronic complications of diabetes and increased mortality, emphasizing the critical significance of achieving glycemic targets. While glycated hemoglobin (HbA1c) is considered the gold standard for determining glycemic management, it has numerous disadvantages, such as a lack of data on glycemic fluctuation or hypoglycemia risk. Moreover, it provides only a single reading, which represents the average of glucose levels over a period of 2–3 months but does not guide change in treatment. Especially, in cases where SMBG readings are discordant with HbA1c, CGM helps identify the actual time when the glucose level is high, low, or within range. Even titrations of dosages of medications is possible by studying the trends and day-night glucose patterns of individual patients with diabetes to control fasting or postprandial glucose levels with much more precision. Thus, with the advent of CGM technology in recent years, glycemic control techniques have progressed beyond HbA1c. They incorporate contemporary glucose metric concepts such as glycemic variability (GV) and time-in-range (TIR) glucose. The professional flash glucose monitoring system is one unique CGM device that generates an ambulatory glucose profile (AGP). This AGP is a collated report that represents several days of glucose data as a 24-h model day format, revealing GV, and highlighting areas which require immediate attention.[9] In contrast to attempting mathematical formulas for deriving GV, a demonstration of GV through this tool helps not only in diagnosis and planning of treatment line for the patient but also as an educational tool to help patients understand their diabetes and thereby take informative actions accordingly. Utilizing AGP obtained via CGM has shown improvement in quality of life by improving glycemic control, lowering the frequency of hypoglycemia through increased opportunity of identification of such events.[10,11] TIR is a simple statistic that indicates the percentage of time that a person's glucose level remains within the specified target range which varies depending on the clinical situation. The primary advantage of these novel CGM measurements over HbA1c is that they enable individualized diabetes therapy through individual-based glycemic control. As an example, use of basal insulin analogs, particularly second-generation basal insulins with extended duration of action and a low risk of hypoglycemia, has showed clinical benefits by lowering GV and increasing TIR demonstrated using CGM.[12] Thus, CGM enables visualization of glycemic profiles and glucose metrics such as GV and TIR, both of which are critical for more effective and precise diabetes treatment.[13,14]

TIR has an inverse relationship with HbA1c, and a lower TIR has been associated with an increased risk of micro- and macrovascular complications of diabetes. Recently, the international consensus on TIR established targets for several diabetes groups. Diabetes can be classified into two major types: Type 1 and Type 2 diabetes, based on the causation and course of affection. Type 1 diabetes mellitus (T1DM), the auto-immune variant, is responsible for 5%–10% of the diabetes cases, whereas Type 2 diabetes mellitus (T2DM), the genetic- or lifestyle-acquired variant, is responsible for around 90%–95% of the diabetes cases. For the majority of persons with T1DM or T2DM, a TIR of >70% (70–180 mg/dL or 3.9–10.0 mmol/L), a time below range (TBR) of 4% (70 mg/dL or 3.9 mmol/L), and a TBR of 1% (54 mg/dL or 3.0 mmol/L) are advised.

At the regulatory level, data linking TIR to risk of diabetic complications could result in TIR becoming a more generally approved endpoint in future clinical trials. TIR, on the other hand, is a poor indication of the frequency or severity of hypoglycemia due to the skewed distribution of potential glucose readings outside the target range. In this article, the current state of knowledge about the linkage of TIR with the risk of developing complications in diabetes is discussed, as well as the inverse relationship between TIR and HbA1c. In addition, the relevance of considering the duration and severity of TBR is highlighted in the discussion of TIR and, by extension, time above range (TAR). TIR >70%, TBR of 4%, and TBR of 1% are suggested targets for the majority of adults with T1DM or T2DM, with less rigorous targets for older or high-risk individuals and in children. As is always the case, glycemic objectives should be tailored to the individual, and nowhere is this truer than in the personal use of CGM and the data it generates.[15-20]

The most prevalent type of diabetes is T2DM. Due to the increased prevalence and consequences of T2DM, additional outcome-based studies are necessary to establish a link between duration in the target range and ongoing risk. These studies provide compelling evidence for the reliability of TIR to identify T2DM individuals at increased risk. The purpose of this article is to highlight the tool of TIR's positioning in India for specific populations/patient profiles that will benefit from the intervention.

Time-In-Range-Glycated Hemoglobin Relationship

There are relatively few data on the TIR targets that have been achieved in patients with T2DM. Beck *et al*. revealed in the multiple daily injections and continuous glucose monitoring in diabetes (DIAMOND) study that 158 T2DM patients receiving Multiple daily Insulin Injections (MDI) increased their TIR from 55.6% to 61.3% after 24 weeks of CGM use.[21] In 2019, Vigersky and McMahon published a meta-analysis indicating that a 10% change in TIR resulted in a 0.8% reduction in HbA1c in a mixed T1DM/T2DM cohort. The study suggested percent TIR as a being important statistic for identifying the endpoint of clinical investigations, projecting the likelihood of diabetic complications, and monitoring an individual patient's glycemic condition.[13] Lu *et al*. confirmed the link between TIR and A1c in a study done at Onduo's virtual diabetes clinic in the United States.[22] The group observed an average TIR of 84% in 194 individuals with T2DM who had an average HbA1c of 7% (53 mmol/mol). From India, Kesavadev *et al*. reported that a TIR of >70% correlates with an A1c level of 7.5% in an Asian Indian population.[23] The majority of

available research has established a linear association between TIR and HbA1c. However, the precise relationship can be more complicated. Interestingly, Lu *et al*. found that GV modifies this association.[22] The study discovered a greater fluctuation in TIR values in patients with T2DM who had a high or low eHbA1c level or an unstable coefficient of variation (CV).

Relationship Between Time-in-Range and Diabetes Complications

Hitherto, only HbA1c has been prospectively tested for predicting diabetes complications. More recently, TIR has also been linked to diabetic complications in multiple studies.[17,24-28] The relationships between TIR of target glucose and TAR estimated from 7-point SMBG but not CGM were initially reported using Diabetes Control and Complications Trial (DCCT) data.[18] To investigate the relationship between 3-day TIR and diabetic retinopathy, Lu *et al*. published a cross-sectional study.[17,24,25] TIR and albuminuria, a marker of cardiovascular risk, were linked to T2DM by Yoo *et al*.[28] In T1DM, Ranjan *et al*. also showed a link between improved TIR and reduced albuminuria.[26] TIR has also been linked to painful diabetic polyneuropathy.[27] However, the relationship of TIR to cardiovascular disease (CVD) is yet to be established. Admittedly, more prospective studies are required on TIR and diabetic complications.

Time-in-Range as a Treatment-Efficiency Metric

Numerous studies have employed TIR as a proxy for blood glucose control while assessing the efficacy of, or comparing, various treatments/interventions for T2DM management [Table 1].[29-31]

Understanding the socioeconomic disparities reflected in a population's varied distribution of T2DM is critical for effective public health interventions. Notably, TIR is a more straightforward dimension for T2DM patients to grasp and comprehend, and it endows them with the ability to maximize their disease self-management. Tan *et al*. examined the association between socioeconomic level (SES) and TIR in 300 T2DM patients classified according to the Socio-Economic Index.[32] The study discovered that patients who were less disadvantaged had a 15% higher TIR than those who were most disadvantaged, demonstrating the efficacy of TIR in addressing inequities in T2DM prevalence and designing patient education and self-management support strategies.

Strategic Positioning of Time-in-Range in Diabetes Care

Given that TIR is a measure of mean glucose across time, how should health-care practitioners position TIR in comparison to established measures of glycemic management (e.g., HbA1c)?[33] TIR is not a substitute for HbA1c testing; rather, it gives information about the overall quality of glucose management. For example, whereas HbA1c normally reflects glucose levels over the preceding 8–12 weeks, TIR can be evaluated over shorter time periods; TIR reflects continuous glucose levels throughout that time period and is susceptible to abrupt changes.[34] As a result of patients with diabetes identifying TIR as having an effect on their quality of life,[15] it may connect more closely with patient experience and patient-reported outcomes.[34] TIR allows for consideration of mean glucose levels in relation to the severity and duration of hypoglycemia (i.e., TBR). There is evidence correlating TIR increases to improved pregnancy outcomes.[35] In addition, TIR may be beneficial when HbA1c levels and mean glucose levels are not in agreement (e.g., chronic kidney disease or hemoglobinopathy). However, specific data from these populations are currently lacking, and alternative approaches to reconciling discrepancies between HbA1c and mean glucose exist that do not require CGM wear (e.g., measurement of fructosamine or glycated albumin, or normalization of HbA1c for mean red blood cell age).[36-38] Similarly, in such conditions, other CGM measurements (e.g., Glucose Management Indicator) may be as useful as TIR at individualizing glycemic objectives. There is a recommendation published by an expert group for the South Asian population given the variance of the diabetes characteristics when compared to the western counterparts.[39] Finally, GV can be a significant impediment to optimizing glucose control and, while the strength of the association is debatable, it has been associated to an increased risk of complications.[40-43] While the GV can be evaluated while examining TIR with CGM, the percent CV is a more precise indicator, with a percent CV of 36% showing stable glucose levels.[44-46]

Time-in-Range and Impact on Diabetes Outcomes

Advances in CGM technology have enabled the development of alternate indices and novel glucose control metrics. TIR has emerged as the favored metric among patients with diabetes. In addition, growing evidence suggests that TIR can be used to predict long-term diabetic problems and pregnancy outcomes. However, for physicians who are primarily familiar with HbA1c and blood glucose measures, it may be challenging to help patients grasp and explain TIR aims, to position TIR in relation to other glucose metrics, and to interpret TIR.[47] The 2017 International Consensus on the Use of CGM by advanced technologies and treatments for diabetes (ATTD), standardized the use of CGM to facilitate therapy adjustments in people with T1DM and T2DM, particularly those who experience frequent hypoglycemia.[46] Prior to the 2017 consensus, different studies used varying time-in-target (TIT) ranges, making comparisons across studies impossible. To account for these variances and conflicts, the ATTD consensus defined hypoglycemia and hyperglycemia as falling into three categories as demonstrated in Figure 1.[45]

Categorizing the time spent in each of the three stages of hypoglycemia and hyperglycemia enables a more precise assessment of severity and enables the most appropriate therapy to be initiated.[45,47]

Table 1: Research literature on time-in-range as a treatment-/intervention-efficiency metric[30-32]

Authors	Sample size	Allocation Methods	Aims	Results
Sofizadeh *et al*.	*n*=124; T2DM patients	Randomized-controlled	To determine whether liraglutide, compared to placebo reduces the HbA1c level for T2DM patients with inadequate glycemic control treated with multiple daily INS injections	Liraglutide enhanced TIR and significantly reduced time with very high glucose levels in the patient population without significantly increasing the risk of hypoglycemia. Hypoglycemia was shown to be more common in MDI-treated T2DM patients with low C-peptide levels and increased GV. Liraglutide's glucose-stabilizing impact was linked to pro-INS
Zheng *et al*.	*n*=20; T2DM patients	Exercise intervention	To see how moderate-intensity aerobic exercise affects blood glucose levels and GV in T2DM patients with DP before breakfast	In T2DM patients, acute moderate-intensity aerobic exercise before breakfast lowered the morning rise in blood glucose, partially counteracting DP. Exercise also helped to lessen blood glucose variations and improve blood glucose management throughout the day. To enhance DP and glycemic management, we propose that T2DM patients with DP engage in moderate-intensity aerobic activity before breakfast
Gao *et al*.	*n*=80; T2DM patients	Open-label randomized trial	To explore the efficacy of ACA and MET on glucose fluctuations as add on therapy in T2DM patients inadequately controlled with premix INS	The combination of MET and ACA with INS successfully decreased blood glucose levels ACA coupled with INS reduced GV when compared to MET
Vianna *et al*.	*n*=97; T2DM patients	Randomized, open-label, active-controlled trial	To determine whether there is a difference in the effects of dapagliflozin and gliclazide MR on GV and glycemic control in individuals with uncontrolled T2DM as measured by CGM	Dapagliflozin improved GV and increased TIR more efficiently than gliclazide-modified release in individuals with T2DM over 12 weeks, as demonstrated by CGM

MET: Metformin, ACA: Acarbose, INS: Insulin, MR: Modified release, CGM: Continuous glucose monitoring, T2DM: Type 2 diabetes mellitus, HbA1c: Glycated hemoglobin, TIR: Time-in-range, DP: Dawn phenomenon, MDI: Multiple dose INS, GV: Glycemic variability

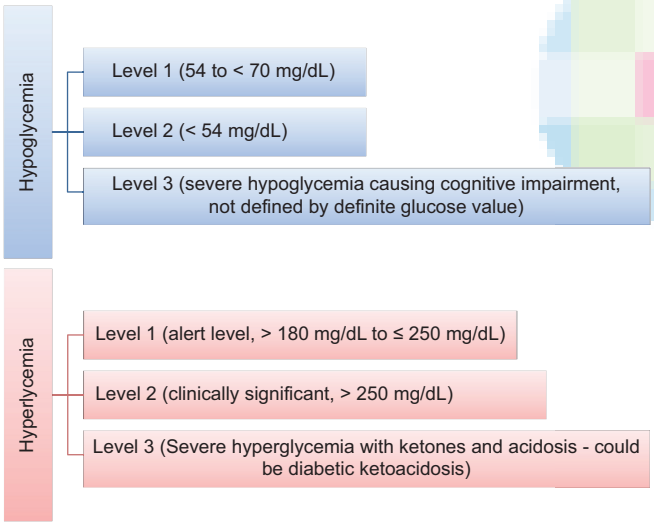

Figure 1: Categorization of hypo- and hyperglycemia as per the ATTD consensus.[46] ATTD: Advanced technologies and treatments for diabetes

The ATTD consensus panel defined TIR as the time spent in the target glucose range of 70–180 mg/dL (3.9–10 mmol/L) for an individual based on glucose measurements.[18] The TIR metric combines three CGM measurements: the percentage of readings and time spent per day above and within target glucose ranges (TAR), within target glucose ranges (TIR), and time spent below target glucose ranges (TIR) (TBR). According to the most recent ATTD international consensus on TIR (2019), the majority of patients with T1DM and T2DM should strive to spend more than 70% of their waking hours (about >17 h) in TIR (70–180 mg/dL), with TBR (70 mg/dL) less than 4% and TAR (>180 mg/dL) <25%.[48]

Petersson *et al*. investigated the connection between TIR and HbA1c in children and adolescents with T1DM using CGM.[49] While TIR was described as being between 70 and 180 mg/dL, TIT was classified as being between 70 and 140 mg/dL. Over a 60-day period, the mean TIR was 60.8% (13.1%), while the mean TIT was 40.9% (standard deviation 12.2%). In addition, a significant nonlinear relationship between TIT and HbA1c was detected throughout the study period. In addition to HbA1c, the study indicated that time spent in TIT could be a relevant indicator for assessing glycemic control.

Beck *et al*. conducted analyses using data from four randomized trials involving 545 persons with Type 1 diabetes who had baseline and 6-month HbA1c values performed by a central laboratory.[33] TIR levels of 70% and 50% (70–180 mg/dL [3.9–10.0 mmol/L]) corresponded to HbA1c values of roughly 7% and 8%, respectively. A 10% increase in TIR (2.4 h per day) resulted in a 0.6% drop in HbA1c, suggesting an inverse link between the two.

Vigersky and McMahon also examined the link between TIR and HbA1c in numerous trials ($n = 1137$), including persons with T2DM.[50] According to the study, for HbA1c objectives of 7% and 6.5%, the percent TIR targets should be roughly 65% and 70%, respectively. According to the study, obtaining a 0.8% (9 mmol/mol) drop in HbA1c required a 10% change in percent TIR.

Apart from assessing patients' glucose control, TIR may be employed as a suitable clinical endpoint in diabetes research.[43]

For instance, TIR is a valid clinical outcome measure for assessing the risk of vascular problems associated with diabetes. TIR appears to be inversely related to the chance of developing vascular problems in diabetics.[43] The expert panel made recommendations for TIR management based on population type and life stage.

Correlation between Time-in-Range, Microvascular, and Macrovascular Outcomes

The DCCT established a strong correlation between HbA1c levels and the risk of diabetes-related chronic vascular complications.[51] Beck *et al*. examined the association between TIR and the development and/or progression of microalbuminuria and diabetic retinopathy using the DCCT trial dataset. For every 10% point decrease in TIR, the risk of developing microalbuminuria increased by 40% (95% confidence interval [CI]: 25–56), while the risk of developing retinopathy progressed by 64% (95% CI: 51–78). This strongly suggests a link between TIR and the risk of developing microvascular complications.[16] Another study examined the relationship between diabetic retinopathy and TIR as measured by CGM in individuals with T2DM. Individuals with advanced diabetic retinopathy had significantly lower TIR and significantly higher GV measurements. In addition, as TIR increased, the prevalence of diabetic retinopathy decreased in severity. TIR was associated with diabetic retinopathy in a negative manner; individuals with T2DM who had vision-threatening retinopathy had the lowest TIR.[17] Diabetic peripheral neuropathy (DPN) complication is another microvascular complication associated with TIR. Mayeda *et al*. found a 43% prevalence of DPN among participants who were within the goal range >70% and <70% of the time.[48] DPN risk increased by 25% with every 10% drop in TIR and conversely as per another study, a 10% rise in TIR showed reduction in severity and prevalence of DPN as well as cardiac autonomic neuropathy.[52] There was no link between HbA1c and DPN symptoms. The study concluded that DPN prevalence is inversely associated to TIR.[52] Similar to diabetic retinopathy and DPN, even diabetic nephropathy has shown inverse association with TIR. Every 10% improvement in TIR also reduces the severity of albuminuria.[52]

Carotid intima-media thickness (CIMT) is a biomarker for subclinical atherosclerosis that can be used to predict incident cardiovascular events. TIR, as assessed by CGM and CIMT, was recently explored as a surrogate marker for CVD in a recent study. T2DM patients with increased CIMT had a substantially lower TIR (P 0.001) than those with normal CIMT. In a fully adjusted model controlling for traditional risk factor of CVD, each 10% increase in TIR was associated with 6.4% lower risk of abnormal CIMT. These findings show that TIR may be associated with macrovascular disease although longitudinal follow-up studies are needed.[25] Thus, TIR has been shown to have direct correlation with both microvascular and macrovascular complications of diabetes [Figure 2].

Difficulties with Widely Used Time-in-Range Glycemic Control Metrics

Clearly, an impediment to widespread adoption of TIRs as the primary way to depict the quality of glucose control is the fact that the majority of persons with diabetes do not utilize CGM technology. Around 25% of Type 1 diabetes patients in India use CGM devices to monitor their glucose levels.[53] Pharmaceutical experts have predicted an anticipated usage of CGM to rise to 50% of T1DM patients in the coming days.[53] Nonetheless, many people with diabetes are unable to utilize or have access to CGM equipment in future, whether by choice or circumstance. For example, even among T1DM Exchange registrants, as recently as 2018, 60%–70% of participants did not use CGM.[54] The investigators examined barriers to device adoption in a subgroup of 1503 adult T1DM Exchange members.[55] Over half of the respondents identified insurance coverage and the cost of equipment and supplies as impediments.[55] Among the modifiable barriers identified by the investigators, the most frequently endorsed reasons for not wearing a device were the "hassle of wearing devices constantly" (47.3% of respondents), "do not like having diabetes devices on my body" (34.8% of respondents), and "do not like how diabetes devices look on my body" (26% of respondents).[55] Hopefully, continued technical advancements such as smaller, cost-effective, and implantable devices will enable some of these challenges to be overcome in the coming years. Allergic reactions to device adhesives can also be problematic for some persons, and more data on this is needed.[56-58] In addition, work needs to be done to increase the acceptability of CGM devices, particularly among certain demographics, such as the developing adult population, which currently has the lowest adoption rates of CGM technology.[55] Similarly, work must be done to close racial and income gaps in CGM use.[54] Although sensor accuracy has increased, it remains imprecise, particularly at sensor glucose levels at their extremes (hypoglycemia or hyperglycemia) or when the rate of change is exceptionally rapid.[59] This may have a specific influence on the TBR debates. The mean absolute relative difference (MARD) between sensor readings and reference blood glucose values is the most often used metric for sensor accuracy, with an arbitrarily a MARD value of <10% generally regarded adequate for insulin dose decision-making.[60] Due to the fact that MARD can be influenced by a variety of factors, including the reference system, the number of paired readings, and the overall research design,[59] it is generally inappropriate to compare manufacturer-reported MARDs between devices. However, in a small study simulating real-world conditions, investigators assessed the accuracy of the Freestyle Libre (Abbott), Dexcom G4 Platinum (Dexcom), and Medtronic Minimed 640G (Medtronic) CGM devices when used concurrently and found that each device's accuracy decreased in the hypoglycemic range (overall MARDs of 13.2%, 16.8%, and 21.4%; MARDs in hypoglycemia).

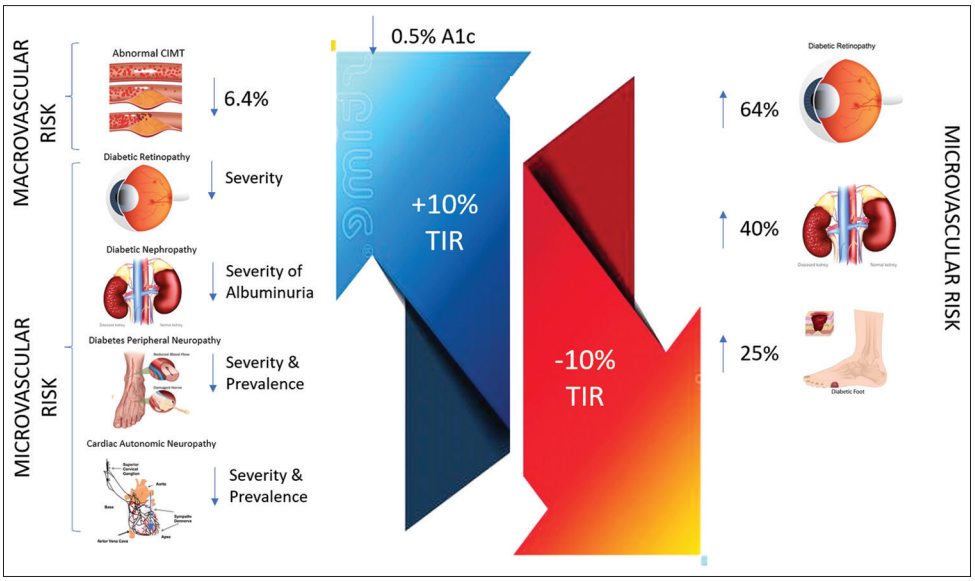

Figure 2: Relationship between time-in-range and diabetes complications[16,25,50-53]

Time-in-Range for Improved Diabetes Outcomes

India is a diabetes hotspot in the world second only to China. Inadequate diabetes control is one of the reasons for the huge burden of diabetes-related complications, and inadequate glucose monitoring is also one of the reasons for poor diabetes control.[61-67] SMBG and HbA1c monitoring technologies both have drawbacks. CGM with TIR has thus emerged as a useful technique for gaining clinical insights into the diabetes control throughout the day. The use of a glucose CGM reader helps to track TIR and also shows glucose highs and lows, glycemic swings, and the impact of diet, lifestyle, and medications on diabetic patients. In both T1DM and T2DM, a lower TIR is linked to a higher risk of vascular problems, whereas a higher TIR is linked to a lower risk of vascular complications. In both TIDM and T2DM, real-world investigations have shown that the faster the CGM scans, the greater the TIR. TIR also empowers people with diabetes to make informed decisions by guiding food and lifestyle choices. TIR measures a patient's clinical response to medicines or insulin. In patients with gestational diabetes or diabetes during pregnancy, TIR aids in achieving glycemic targets and thus improves outcomes both for the mother and the fetus. TIR is thus a motivational and instructional tool for patients with diabetes of all types.[68,69]

Poor perioperative blood glucose control is related to poor outcomes in patients undergoing heart surgery. Numerous glycemic targets have been recommended in order to decrease wound infection and overall death rates. Omar *et al*. conducted prospective research to assess glucose management in patients with or without diabetes following heart surgery.[70] The patients' glycemic goal was 6.0-8.1 mmol/L, as assessed by TIR. Patients with >80% TIR showed better outcomes in terms of wound infection (P = 0.05), length of hospital and intensive care unit (ICU) stay (P = 0.03 and P = 0.04, respectively), and duration of ventilator uses (P = 0.03), as compared to patients with 80% TIR.

Randomized trials demonstrate that CGM improves neonatal health outcomes as well as maternal glucose control. Throughout pregnancy, the goal is to raise TIR while decreasing TAR and TBR. In the second and third trimesters, a 5% decrease in TIR and a 5% increase in TAR are related with an increased risk of neonatal hypoglycemia, large-for-gestational-age neonates, and neonatal ICU admission. Therefore, a TIR of >70% (16 h, 48 min) and a TAR of 25% (6 h) should be targeted as early in pregnancy as possible, for optimal neonatal outcomes.[35]

TIR has a significant advantage over HbA1c in that it can be evaluated on a near-hourly basis: interpreting glycemic control in terms of TIR provides a more nuanced, cause-and-effect understanding of glucose fluctuations. One can identify the behaviors and choices that contribute to out-of-range glucose levels and determine where/when changes can be made prospectively. TIR is more accessible and intuitive from the perspective of people with disabilities. For example, in a survey of 3461 person with diabetes, TIR was identified as the primary outcome measure that has a "significant impact" on daily life with diabetes because it reflects priorities of patients with diabetes and can be used to quantitatively evaluate treatment efficacy.[15]

The international guidelines laid down for the first time by ATTD in June 2017, for implementing TIR for clinical practice in diabetes, have been a landmark in monitoring space in diabetes.[45] The same has been endorsed by the most-esteemed medical bodies namely American Diabetes Association (ADA), European Association for the Study of Diabetes, International Society for Pediatric and Adolescent Diabetes, and others, increasing the reliance on the same.

However, there are an array of factors that differentiate the Indian population from the western counterparts, ranging from Asian-Indian phenotype, cultural and geographical differences, diet and lifestyle differences, etc.[71,72] This sometimes poses a challenge to apply these international guidelines to Indian population. The clusters of Type 2 diabetes in India are different from the West.[73] As mentioned earlier in this article, an expert group has worked up recommendations specifically for the South Asian group keeping in mind the above differences. This article is the first one to talk about the frequency of measuring TIR with a minimum of bi-annually for patients with comparatively good glycemic control [Figure 3].

Moreover, the utility of TIR can be potentially leveraged in distinct targeted populations such as newly diagnosed diabetes and uncontrolled diabetes patients on oral anti-diabetic agents with elevated HbA1c levels to be started on insulin to identify silent hypoglycemia in gestational DM or diabetes with pregnancy and for adjusting diet and lifestyle management and appropriate glucose monitoring in pre- and posthospitalization [Figure 4].

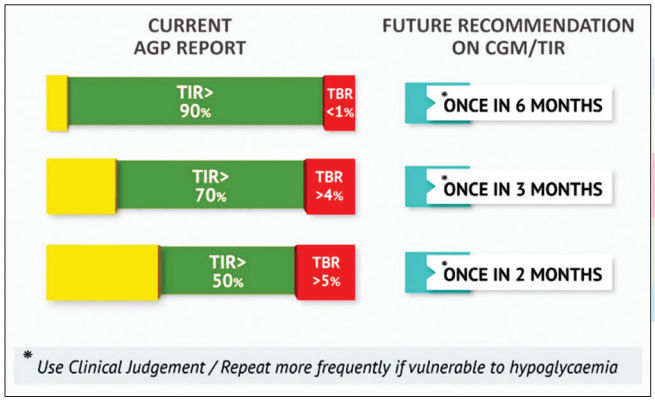

Figure 3: Recommended frequency for repeating CGM/TIR assessment in patients with Type 2 diabetes in South Asia. CGM: Continuous glucose monitoring, TIR: Time-in-Range

Potential Patient Profiles for Adopting Time-in-Range to Achieve Optimal Glucose Control

While TIR has been seen beneficial across types and stages of diabetes, there are select patient profiles that may benefit from adopting this metric to achieve optimal glycemic control.

1. Oral anti-diabetic (OAD) inadequacy – This includes patients who have been on maximized doses of OADs agents for quite some time and yet uncontrolled, leaving them insulin as the last resort. Sometimes, even though OADs are not maximized, patients may have fear of insulins and would wish to delay the initiation as much possible
2. Hypoglycemia in patients on insulin – In India, premixed insulin dominates the insulin usage for diabetes management. The popularity of the premixed insulins predisposes the patients to hypoglycemia. A large proportion of patients develop hypoglycemia unawareness by the time they reach 10–15 years of diabetes and hence, hypoglycemia remains undiagnosed
3. Gestational DM or pregnancy in diabetes – Pregnancy is a metabolic stress for a human body and with diabetes poses an array of challenges for the hormones to cause huge degree of glucose fluctuations to meet the increased metabolic demands. At the same time, the pregnancy outcome is always very crucial for the parents; hence, tight glucose control becomes vital both before and especially during pregnancy
4. Diet and lifestyle management for glucose control – Diet and lifestyle modification are inevitable of all forms of diabetes management. However, some patients find it easy, while some difficult to adopt changes suggested by their diabetes educator/counselor or physician/diabetologist/endocrinologist. Enabling to visualize the impact of dietary and lifestyle changes by using CGM and TIR made will help empower and motivate the patients to manage their diabetes on their own

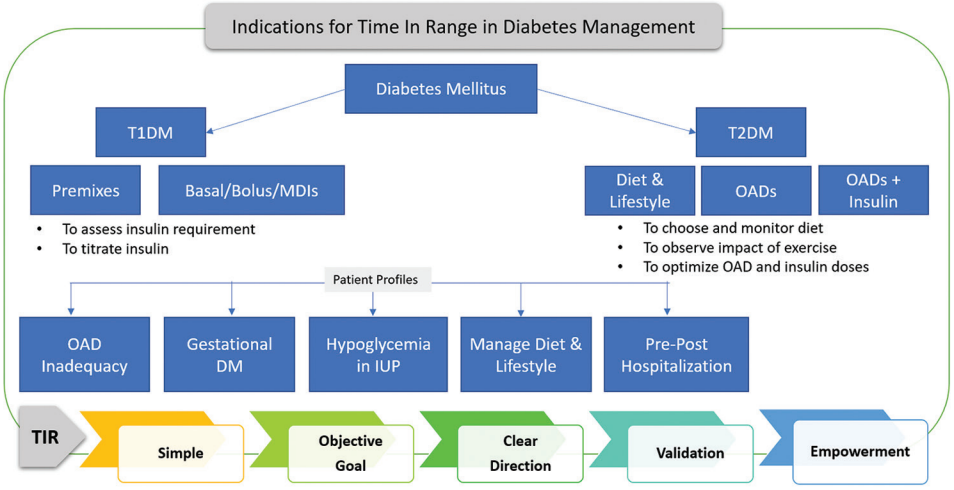

Figure 4: Indications of time in range in diabetes management. T1DM: Type 1 diabetes mellitus, T2DM: Type 2 diabetes mellitus, TIR: Time-in-Range

5. Pre and post-hospitalization – Patients with diabetes have to deal with hospitalization quite often. Good glucose control is critical to ensure faster recovery of patients. In medical causes for admission, glucose control may decide the number of days in hospital basis recovery; whereas in surgical cases, glucose control determines the decision to proceed with the surgery and for better postsurgical outcomes.

Thus, the adoption of TIR using CGM in the above-mentioned cases is a strategic move toward improving clinical outcomes in diabetes in Indian patients in a precisely targeted manner. It also follows the path shown by ADA which suggests including patients to own up responsibility within the diabetes case continuum.

Conclusion

Adoption of CGM technology is rapidly occurring worldwide and in India. By continuously monitoring glucose levels, the basic CGM parameters including TIR allowed for a more thorough understanding of an individual's glycemic condition. This has aided both clinicians and patients in making more informed treatment decisions than when the HbA1c alone was used. TIR is an excellent addition to HbA1c as it contains additional information and can also indicate the percentage of glycemic control day. Although prospective studies are scarce, evidence suggesting TIR's ability to predict diabetic complications is rapidly emerging. To overcome hurdles to CGM use, sustained efforts are required. We anticipate that CGM measurements, particularly TIR, will be increasingly adopted in clinical practice.

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Conflicts of interest

There are no conflicts of interest.

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