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Review article

Time-in-range as a target in type 2 diabetes: An urgent need

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ABSTRACT

Time-in-range emerged as a valuable blood glucose metric, 'beyond HbA1c' for a deeper insight into glycemic control in people with diabetes. It denotes the proportion of time that a person's glucose level remains within the desired target range (usually 70–180 mg/dL or 3.9–10.0 mmol/L). Though clinical targets in the current recommendations for type 1 and type 2 diabetes are close enough, their clinical profiles and prevalences are quite different.

Type 2 diabetes is the commonest form of diabetes. Many clinical trials have challenged the usefulness of HbA1c as a glycemic target for Type 2 diabetes mellitus. On account of the higher prevalence and complications of type 2 diabetes, more outcomes-based studies are needed to associate time-in-range with its ongoing risk. These studies strongly support the dependability of time-in-range to identify patients with elevated risk in type 2 diabetes. We discuss the utility of time-in-range, a new metric of continuous glucose monitoring as an outcome measure to correlate with type 2 diabetes risks and complications and to analyze the effectiveness of type 2 diabetes management. This approach may support the use of time-in-range as a metric for long-term health outcomes in the type 2 diabetes population.

1. Introduction

Time-in-range (TIR) is an intuitive metric that denotes the amount of time in percentage that a person's glucose level remains within the proposed target range (3.9–10.0 mmol/L (3.5–7.8 mmol/L in pregnancy) or 70–180 mg/dL (63–140 mg/dL in pregnancy) [1, 2]. The concept of TIR has emerged from the efforts of diabetes experts to discover a reliable parameter, "beyond HbA1c" to assess glycemic control. According to the International consensus on time-in-range, TIR should be considered as the key CGM-derived metric defining short-time glycemic control, since it delivers more actionable data than HbA1c alone. The panel also established specific target ranges identifying different diabetes populations such as pregnancy and high-risk groups. It was estimated that a type 1 or type 2 individual should spend more than 70% (16 h, 48 min) of a day in the target range while more than 50% (>12 h) is applicable for older and high-risk type 2 patients [1]. An effective treatment should always target to increase TIR while reducing Time-below-range (TBR).

HbA1c analysis that reflects the average glucose level has been considered as the gold standard for evaluating glycemic control. But it fails to represent accurate glycemic control in many circumstances since it is influenced by numerous factors other than glucose concentration [3]. Patients with similar A1c values show considerable differences in their glucose profiles. Alongside, HbA1c fails to indicate glycemic variability (GV): daily glycemic excursions that may contribute to risks of hypo- and hyperglycemia which have been allied to the development of micro-and macrovascular complications in diabetes [4]. Four long-term, randomized, open-label trials: UKPDS 33, Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE), and the Veterans Affairs Diabetes Trial (VADT) demonstrated that intensive glycemic control (HbA1c target of 6.3%–7.4%) does not reduce the incidences of macrovascular events and mortality in Type 2 diabetes (T2D) patients further challenging the credibility of HbA1c as a therapeutic target for T2D [5, 6, 7, 8, 9]. Diabetes experts have been endeavouring to shift the focus from HbA1c alone to a more glucose-centric and patient-centric metric. With the increasing popularity of continuous glucose monitoring (CGM), TIR has been evolving as the principal metric for appraising complications of diabetes. Earlier studies have concluded that each 10% increase in TIR corresponds to ~0.5% HbA1c reduction in both Type 1 diabetes (T1D) and T2D patients [10, 11]. TIR, even in the

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nondiabetic range was associated with better patient outcomes [12]. Quite a few studies have correlated TIR with diabetes risk factors and complications. These evidences supported % TIR as an important outcome variable of glycemic control in clinical trials and diagnostic practice [13].

Since a majority of diabetes patients have T2D, with the number snowballing quickly on a global scale, any new glycemic metric should be tested for its effectiveness to associate with T2D complications to replace the long-standing HbA1c. T2D patients are more susceptible to developing endothelial dysfunction, oxidative stress, and cardiovascular disease, attributed to GV [14]. The severity and incidence of GV in T2D patients can be controlled by improving TIR. Beck *et al* showed that individuals with T2D could improve their TIR by 10.3% after 24 weeks of CGM initiation [15]. Even though few recent studies have reported that TIR may better capture risks of micro- and macrovascular complications in patients with T2D, it is still debatable that whether improving TIR can alleviate these risks. Therefore, given the current controversy, we provide a comprehensive review of the available evidence on the performance of TIR as a diagnostic marker for the detection and management of complications in T2D.

2. Implications for T2D management and population screening

'International Consensus on Use of Continuous Glucose Monitoring' convened at the Advanced Technologies & Treatments for Diabetes (ATTD) Congress 2017 recommended the use of Time-in-range in clinical diagnosis as a measure of short-time glycemic control in both T1D and T2D.

Recommendations are given below:

1. Percentages of time in ranges (target, hypoglycemia, and hyperglycemia) should be measured and reported.
2. Different TIRs in combination with a GV measure should be reported as key diabetes control metrics in clinical studies [13].

The recommended levels of target percentages of time in different glycemic ranges specific for different T2D populations including high risk, elderly and pregnant patients with T2D are summarized in Table 1. Even though these recommendations would facilitate logical and safer therapeutic decision making, it is mandatory to appraise the in-depth utility of TIR in real-world clinical practices.

2.1. Relationship between TIR and HbA1c

To date, very few data are presented on the magnitude of TIR attainable in patients with T2D. In Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes (DIAMOND) trial, Beck *et al* substantially demonstrated that 158 T2D patients (mean age:60 ± 10 years) receiving multiple daily injections (MDI) of insulin had improved their TIR from 55.6% to 61.3% after 24 weeks of CGM initiation [15]. Evidence on how TIR relate to clinical outcomes in T2D management have materialized from some of the most recent studies. In 2019, a meta-analysis by Vigersky and McMahon reported that every 10% change in TIR, resulted in a 0.8% change in HbA1c in a mixed type 1/type 2 diabetes population. The study proclaimed the prospects of %TIR as a preferred metric for determining the endpoint of clinical studies, forecasting the risk of diabetes complications, and measuring the glycemic status of an individual patient [10]. A study conducted by Lu J *et al* at Onduo's Virtual Diabetes Clinic (VDC), USA, reinforced the correlation between TIR and A1c. The group observed a mean TIR of 84% in 194 T2D patients with a mean HbA1c of 7% (53 mmol/mol) [16]. In line with the international consensus, Kesavadev *et al* revealed that a TIR of >70% relates to an A1c level of <7.5% in a population of Asian Indians [17]. Majority of these existing studies have reported a linear relationship between TIR and HbA1c. But the exact association can be more complicated. Interestingly Lu J *et al* observed that GV has a modifier effect on this relationship. The study reported a higher variability of TIR values in T2D patients in the high-or low-range of eHbA1c or unstable coefficient of variation (CV) [18].

These studies suggest that TIR should transform as a strong target and predictor of diabetes complications and should be a daily routine in diabetes care. The correlation of A1c for a given TIR level based on these T2D analyses is comprised in Table 2. Similar analyses are required in populations of different origins as the demographic and biochemical profiles of T2D vary significantly among global populations. Combining information from populations of diverse ancestry in large, trans-ethnic meta-analyses will permit a profound inspection of the transferability of TIR to multiple ethnicities. However, data specifically addressing older/high-risk and pregnant individuals in this context are still inadequate.

2.2. TIR as a metric of treatment/intervention efficiency

Multiple studies have used TIR as an indicator of blood glucose control while evaluating the efficiency or comparing different treatments/interventions for T2D management. Gal *et al* assessed the feasibility of remote CGM initiation in 7 T2D patients, successfully exploiting TIR as an outcome measure [19]. Sofizadeh *et al* measured the effect Liraglutide, a glucagon-like peptide-1 (GLP-1) receptor on glycemic control in 124 T2D patients treated with MDI in terms of time-in-hypoglycaemia, time-in-hyperglycaemia, and time-in-range. Liraglutide treatment group spent more time in the target glucose levels and

Table 1. Classification table on the recommended level of time in range for different category of patients with T2D [1, 32].

Category of T2D	Recommended Time-in-Range	
	Recommended level of Blood glucose	Required time
Generalized	70–180 mg/dL or 3.9–10.0 mmol/L	>70% (>16 h 48 min)
	<70 mg/dL or <3.9 mmol/L	<4% (<1 h)
	<54 mg/dL or <3 mmol/L	<1% (<15 min)
	>180 mg/dL or >10 mmol/L	<25% (<6 h)
	>250 mg/dL or >13.9 mmol/L	<5% (<1 h, 12 min)
Older/High risk	70–180 mg/dL or 3.9–10.0 mmol/L	>50% (>12 h)
	<70 mg/dL or <3.9 mmol/L	<1% (<15 min)
	>250 mg/dL or >13.9 mmol/L	<10% (<2 h, 24 min)
Pregnancy Type 2/Gestational Diabetes mellitus	63–140 mg/dL or 3.5–7.8 mmol/L	>85% (20 h, 24 min)
	<63 mg/dL or <3.5 mmol/L	<4% (<1 h)
	<54 mg/dL or <3 mmol/L	<1% (<15 min)
	>140 mg/dL or >7.8 mmol/L	<10% (<2 h, 24 min)
People with Frail Diabetes	70–180 mg/dL or 3.9–10.0 mmol/L	>50% (>12 h)
	<70 mg/dL or <3.9 mmol/L	<1% (<15 min)
	>250 mg/dL or >13.9 mmol/L	<10% (<2 h, 24 min)

Table 2. Correlation between TIR (70–180 mg/dL or 3.9–10.0 mmol/L) and HbA1c as estimated by studies.

Authors	Type of population	Correlation Coefficient (r), between TIR and HbA1c
Vigersky and McMahon	Mixed type 1/2 (n = 1,137)	−0.84
Dixon FR *et al*	Type 2 (n = 194)	−0.78

less time at very high glucose levels [20]. Similarly, Zheng *et al* showed the effect of moderate-intensity aerobic exercise before breakfast, an intervention strategy adopted to manage the dawn phenomenon (DP) in 20 type 2 diabetes patients using TIR. The intervention was found to increase the TIR to 90.75 ± 12.27% compared to 83.5 ± 15.41% before exercise [21]. Gao F et al., utilized TIR along with HbA1c to evaluate the effect of Acarbose (ACA) or metformin (MET) combined with premixed insulin (INS) on glycemic control [18].

Vianna *et al* utilized the improvements in TIR and GV as a measure to compare the effects of dapagliflozin and gliclazide modified release (MR) in 97 participants (median age: 57.9 ± 8.7 years) with uncontrollable T2D. The data suggested that in the dapagliflozin group TIR was increased by 24.9% from baseline and in the gliclazide MR group the increase was 17.4 %. GV measured by the CV% was significantly improved by 3.8% in the gliclazide MR group and did not show any difference in the dapagliflozin group (0.7%). Both groups exhibited no significant change in the % of HbA1c from the baseline (dapagliflozin group: -1 % and gliclazide MR group: -1.3%). The study established %TIR as a promising metric for comparison of two different therapeutic agents in diabetes [14].

Understanding the socio-economic inequalities observed in the heterogeneous distribution of T2D in a population is essential for contributing effectively to public health interventions. Notably, TIR is a simpler dimension for T2D patients to understand, comprehend, and bequeaths the power to optimize the self-management of the disease. Tan *et al* investigated the link between socioeconomic status (SES) and TIR in 300 T2D patients categorized based on the Socio-Economic Index. The study revealed that the least disadvantaged group of patients was associated with a 15% higher TIR compared to the most disadvantaged group and asserted the efficacy of TIR to discourse the disparities in T2D prevalence and developing patient education and self-management support plans [22].

3. Implications for prediction of risk of T2D complications

At present research-based evidence on the association between TIR as an outcome variable of glycemic control and T2D-related micro- and macrovascular complications is scarce.

Omar *et al* have earlier shown that patients with >80% TIR, irrespective of the diabetes status, achieved better clinical outcomes [12]. A study by Lu J *et al* reported that TIR assessed by using CGM had a negative association with all stages of diabetic retinopathy (DR) (graded as non-DR, mild non-proliferative DR (NPDR), moderate NPDR, or vision-threatening DR) in patients with T2D. The findings suggested that the severity of DR decreased with a progressive increase in TIR. The study also found that the association between TIR and DR is independent of HbA1c and GV metrics [23]. Mayeda *et al* studied the relationship between TIR and diabetic peripheral neuropathy (DPN) among 105 T2D patients with moderate-to-severe chronic kidney disease (CKD). Lower TIR and higher Glucose Management Indicator (GMI) were found to be associated with DPN symptoms and prevalence. For those patients with a TIR >70%, DPN prevalence was estimated as 43% whereas for those with a TIR <70%, the prevalence was 74% and every 10% reduction in TIR was linked with a 25% increased risk of DPN. Most importantly, the study

Table 3. Research Literature on the association of TIR with micro- and macrovascular complications.

Authors	Sample Size & Mean Age	Research methods	Aims	Results and Conclusion
Jingyi Lu *et al.*, 2018	N = 3262 &Age = 60.4 ± 12.0 yrs	Retrospective study	To investigate the association between TIR and diabetic retinopathy (DR) among T2D patients.	Prevalence of DR by severity decreased with increase in TIR. The association of TIR with DR was independent of HbA1c and GV.
Laura Mayeda *et al.*,2020	N = 105 &Age = 68	Prospective observational cohort study	To find out the association between TIR and diabetic peripheral neuropathy (DPN) symptoms among patients with T2D and moderate-to-severe Chronic Kidney Disease.	The prevalence of DPN was inversely correlated with TIR. For participants who with a target range >70%, DPN prevalence was 43%, and those who were within the target range <70%, DPN prevalence was 74%.
Jingyi Lu *et al.*, 2020	N = 2215 &age 59.15 ± 11.8 yrs	Cross-section analysis	To investigate the association of TIR with carotid intima-media thickness (CIMT), a surrogate marker of cardiovascular disease (CVD).	Patients with abnormal CIMT has lower TIR. A 10% increase in TIR was associated with a 6.4% lower risk of abnormal CIMT.
Qingyu Guo *et al.*, 2020	N = 349& age = 48.28 ± 13.39 yrs	Retrospective	To understand the relationship between TIR and cardiovascular autonomic neuropathy (CAN) in individuals with T2D.	TIR is inversely associated with a total score of CAN independent of HbA1c and GV metrics.
Jee Hee Yoo *et al.*, 2020	N = 866	Retrospective	To investigate the association between the CGM-derived TIR, hyperglycemia, hypoglycemia metrics, and albuminuria.	Prevalence of albuminuria is lesser in T2D subjects with the recommended level of TIR and TAR. An odds ratio of having albuminuria was 0.94 per 10% increase in TIR.
Jingyi Lu *et al.*, 2020	N = 2893	Cross-sectional study	To study the associations of multiple prespecified TIR levels with carotid intima-media thickness (CIMT) and diabetic retinopathy (DR) in T2D patients.	TIRs with the upper limit from 140–150 to 200 mg/dL (7.8–8.3 to 11.1 mmol/L) were significantly correlated with abnormal CIMT and DR.

did not find a significant association with HbA1c and DPN symptoms [24].

In a group of 349 Chinese T2D patients, the proportion and prevalence of severe cardiovascular autonomic neuropathy (CAN) were reversely associated with TIR independent of HbA1c and GV metrics. Here the patients were grouped based on cardiac autonomic reflex tests (CARTs) as absent CAN, early CAN, definite CAN, and severe CAN. Results indicated that the patients with a lower presence of CAN spent significantly more time (TIR >83%) in the target range [25]. Lu J *et al* investigated the association between TIR and carotid intima-media thickness (CIMT), a surrogate marker of cardiovascular disease (CVD) in 2215 T2D patients. The study revealed that patients with normal CIMT had a higher TIR compared with those with abnormal CIMT and a 10% increase in TIR was associated with a 6.4% reduced risk of abnormal CIMT [26]. In another important study, Lu J et al addressed the associations of various prespecified TIR levels with CIMT and DR in a large type 2 diabetes population. They observed a significant correlation between TIR with the upper limit from 140-150 to 200 mg/dL and abnormal CIMT and DR [27].

Yoo *et al* observed that TIR and hyperglycemia metrics are strongly associated with albuminuria in T2D. The prevalence of albuminuria was low in T2D patients who attained the required targets of TIR 70–180 mg/dL, time above range (TAR) > 180 mg/dL, and TAR >250 mg/dL. The study reported the odds of the occurrence of albuminuria as 0.94 with a10% increase in TIR [28].

Li C *et al* investigated the frequency of dawn phenomenon (DP) and its relationship with time in range (TIR) and glycemic variability (GV) in diabetes patients with normal glucose tolerance, impaired glucose regulation, and newly diagnosed T2D. TIR was significantly lower in the DP group [29].

These studies undoubtedly prove TIR as an instinctive metric of glycemic control to associate with complications in T2D. But it is still to be proved that whether measuring TIR alone will reflect a comprehensive assessment of T2D diagnosis and management. Notably, some of the studies mentioned above suggested that the usefulness of TIR in envisaging the risk of T2D complications is independent of HbA1c and GV metrics. However, more data are needed to evaluate the relationship between TIR and diabetes complications. Table 3 summarizes the literature on the association of TIR with various T2D complications.

3.1. Challenges in implementing time-in-range as a glucose metric

The key challenges in accepting TIR are the high cost of CGM and unavailability of the latest and more accurate devices in some parts of the world. Barriers to uptake include cost (the high cost to procure sensors and replacing system parts as well as lack of insurance coverage), technical issues (variability in sensor performance), human factors issues (inconvenience due to wearing a device continuously), absence of a standardized format for displaying results, and lack of understanding or consensus on how to exploit CGM data to make therapeutic decisions [30]. The suboptimal number of studies correlating TIR and micro-and macrovascular complications in diabetes has been another concern [31].

Lack of effective diabetes education programs to support the physicians and patients in CGM data analysis and better interpretation of the TIR data is another limitation [1]. To date, the training programs have been focusing on the technical aspects of the devices rather than the optimal usage of the indices, especially TIR, to improve diabetes care [30]. Training programs have an integral role in implementing TIR as a useful clinical measure that complement HbA1c in daily treatment decision making.

4. Conclusion

The idea of time-in-range has challenged the conventional viewpoint of using HbA1c as a "one-size-fit-all" screening tool for diabetes management. Numerous studies have explored the utility of TIR in clinical practice and trials for T1D management. Even though targets for T1D and T2D are intimate, their clinical/biochemical profiles and demographic prevalence vary considerably. Though limited in number, studies have substantively demonstrated the potential of TIR as a patient-centric metric for glycemic control in type 2 diabetes. Despite its proven value, the clinical utilization of TIR for T2D management has remained suboptimal. Its implications on treatment effectiveness, risk stratification, and complications in T2D have already shown. The power of the association of TIR with other clinical endpoints in T2D management and risk factors seems to be of the comparable degree to that of HbA1c. Based on these conclusions, a persuasive case can be forwarded that TIR has a robust association with micro- and macrovascular complications and should be positioned as an endpoint and valued metric for T2D management. But there is a knowledge gap in understanding whether TIR can be related to T2D risks independently of the other clinical targets. Future studies are warranted to acquire a conclusive sketch of the function of TIR in T2D management and the onset/progression of its complications.

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The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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