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REVIEW

Positioning time in range in diabetes management

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Abstract

Recent upswings in the use of continuous glucose monitoring (CGM) technologies have given people with diabetes and healthcare professionals unprecedented access to a range of new indicators of glucose control. Some of these metrics are useful research tools and others have been welcomed by patient groups for providing insights into the quality of glucose control not captured by conventional laboratory testing. Among the latter, time in range (TIR) is an intuitive metric that denotes the proportion of time that a person's glucose level is within a desired target range (usually 3.9–10.0 mmol/l [3.5–7.8 mmol/l in pregnancy]). For individuals choosing to use CGM technology, TIR is now often part of the expected conversation between patient and healthcare professional, and consensus recommendations have recently been produced to facilitate the adoption of standardised TIR targets. At a regulatory level, emerging evidence linking TIR to risk of complications may see TIR being more widely accepted as a valid endpoint in future clinical trials. However, given the skewed distribution of possible glucose values outside of the target range, TIR (on its own) is a poor indicator of the frequency or severity of hypoglycaemia. Here, the state-of-the-art linking TIR with complications risk in diabetes and the inverse association between TIR and HbA_{1c} are reviewed. Moreover, the importance of including the amount and severity of time below range (TBR) in any discussions around TIR and, by inference, time above range (TAR) is discussed. This review also summarises recent guidance in setting 'time in ranges' goals for individuals with diabetes who wish to make use of these metrics. For most people with type 1 or type 2 diabetes, a TIR >70%, a TBR <3.9 mmol/l of <4%, and a TBR <3.0 mmol/l of <1% are recommended targets, with less stringent targets for older or high-risk individuals and for those under 25 years of age. As always though, glycaemic targets should be individualised and rarely is that more applicable than in the personal use of CGM and the data it provides.

Keywords CGM · Diabetes complications · HbA_{1c} · Hyperglycaemia · Hypoglycaemia · Review · Time below range · Time in range

Abbreviations

CGM	Continuous glucose monitoring (or continuous glucose monitor)
CSII	Continuous subcutaneous insulin infusion
DIAMOND	Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes (study)
GMI	Glucose management indicator
isCGM	Intermittently scanned continuous glucose monitor
MARD	Mean absolute relative difference
PRO	Patient-reported outcome
rtCGM	Real-time continuous glucose monitor
SMBG	Self-monitoring of blood glucose
TAR	Time above range
TBR	Time below range
TIR	Time in range

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Introduction

When the Diabetes Control and Complications Trial (DCCT) first demonstrated that intensive glucose lowering reduces the risk of long-term diabetes complications, intensive glucose control involved self-monitoring of blood glucose (SMBG) at least four times daily, a weekly blood glucose check at 03:00 hours and regular laboratory measurement of HbA_{1c} [1]. Today, over a quarter of a century on, emphases on individualised care and advances in glucose monitoring

technology have provided access to a wealth of alternative indices of glucose control quality that are available to individuals who have the means and desire to make use of continuous glucose monitoring (CGM) technologies. Among these metrics, time in range (TIR) has surfaced as a measure that is preferred by patients because of its bearing on daily life [2]. Concurrently, evidence is beginning to emerge indicating that TIR can predict the risk of long-term diabetes complications [3, 4] and pregnancy outcomes [5, 6]. However, for clinicians and researchers who are most familiar with evidence supported by blood glucose measurement and HbA_{1c}, it may be difficult to know how to interpret TIR, where to position TIR relative to other glucose metrics and what TIR goals to discuss with patients. In this short review, I summarise the state-of-the-art for TIR, emphasising that TIR is largely determined by the extent of hyperglycaemia and that any discussions around TIR goals should include consideration of time below range (TBR) as well. I summarise recent guidance for healthcare professionals in helping patients interpret TIR goals and I consider the obstacles currently limiting the broad application of TIR in diabetes management.

Advances in CGM use and the emergence of TIR as a key metric of glucose control

Modern use of CGM in clinical practice began in 2000 [7], although its widespread adoption has accelerated more rapidly in the past few years. For instance, among T1D Exchange participants, the percentage of individuals making use of CGM technology increased from 7% in 2010–2012 to 30% in 2016–2018 [8]. There are several reasons underlying this increase in CGM uptake, including improvements in sensor accuracy, regulatory approval of CGM devices for non-adjuvant use and a reduced need (or no need) for fingerstick calibration [7]. Existing CGM systems fall into several categories: (1) retrospective CGM (professional, masked to the user at the time of wear); (2) real-time CGM (rtCGM; personal, unmasked); and (3) intermittently scanned CGM (isCGM; also called 'flash' CGM) [7, 9]. A growing body of evidence (summarised elsewhere [10, 11]) supports the advantages of CGM technology in improving glycaemic control. For individuals with type 1 diabetes, rtCGM use (combined with either continuous subcutaneous insulin infusion [CSII] or multiple daily injections of insulin) is associated with a lowering of HbA_{1c}, a shortened duration of time in hypoglycaemia and a reduction in moderate-to-severe hypoglycaemia [11]. rtCGM has also been shown to be associated with reductions in HbA_{1c} in individuals with type 2 diabetes, without increasing the frequency of hypoglycaemia [12, 13]. isCGM has been associated with reduced time spent in hypoglycaemia in individuals with type 1 or type 2 diabetes [14, 15].

CGM data can be accessed by individuals in real-time on personal devices and curated personal data can be viewed using proprietary software packages (e.g. Dexcom CLARITY, Glooko/Diasend, CareLink, LibreView) or open source software (e.g. Nightscout, Tidepool). The data analysis tools offer patients and healthcare professionals a wide range of metrics of glucose control quality, including number of days worn, percentage of time CGM is active, mean glucose, glucose management indicator (GMI; formerly estimated HbA_{1c} [16]), glycaemic variability (%CV) and TIR [17]. Some of these parameters (e.g. %CV) can be conceptually abstract, whereas others (e.g. TIR) are more intuitive and accessible to patients. For example, in one survey of 3461 participants, TIR ranked second, only behind food choices, on factors that participants considered to have a 'big impact' on daily life with diabetes [2].

TIR definitions

In considering TIR definitions and thresholds it is important to distinguish TIR from 'time in ranges'. TIR refers to the amount of time glucose levels fall within a target range (typically between 3.9 mmol/l and 10.0 mmol/l), whereas 'time in ranges' encompasses TIR, time above range (TAR) and TBR [17]. It is worth emphasising here that a target of 3.9–10.0 mmol/l represents a broader range of glucose values than those that occur in populations that do not have diabetes. The normal glucose range for individuals without diabetes is usually reported as being between 3.9 mmol/l and 7.8 mmol/l [18]. However, in one recent study that included 847,847 US veterans without diabetes, the 5% and 95% percentiles for median random plasma glucose were 4.6 mmol/l and 6.8 mmol/l, respectively [19]. Thus, the upper and lower limits for determining TIR are not synonymous with the upper and lower limits of 'normal' glucose values. Rather, the choice of the upper and lower glucose thresholds for determining TIR is (at least partly) pragmatic. Outside of the pregnancy setting, most individuals with type 1 diabetes are unable to spend most of the day with glucose levels in the 3.9–7.8 mmol/l range [18]. Instead, the upper limit for determining TIR has been set at 10.0 mmol/l to align with the recommended target upper limit for peak postprandial glucose levels for people with diabetes [20]. The lower limit for determining TIR (glucose 3.9 mmol/l) reflects the upper limit of the definition of hypoglycaemia, the point at which counter-regulatory hormone release generally begins to occur [18]. For determination of TAR, hyperglycaemia is subdivided into level 1 (glucose 10.1–13.9 mmol/l) and level 2 (glucose >13.9 mmol/l); for determination of TBR, hypoglycaemia is subdivided into level 1 (glucose 3.0–3.8 mmol/l) and level 2 (glucose <3.0 mmol/l) [17, 18]. The subdivision of hypoglycaemia and hyperglycaemia into different levels is based on recent consensus recommendations as to the adverse consequences of glucose levels <3.0 mmol/l (decreased

symptom awareness, increased risk of severe hypoglycaemia, increased mortality risk) [18, 21] or >13.9 mmol/l (increased risk of diabetic ketoacidosis, higher likelihood of long-term complications) [18]. Different glucose thresholds for determining TIR are applied in pregnancy (3.5–7.8 mmol/l), with an upper limit of 7.8 mmol/l aligning with the 1 h post-meal glycaemic threshold target for pregnancy [22] and a lower limit of 3.5 mmol/l based on levels safely achieved in recent clinical trials [5, 6, 17]. Time in ranges can be expressed as either the percentage of readings in each range per day or the mean number of hours and minutes spent in each range per day, or both [17].

Evidence linking TIR to the risk of long-term diabetes complications

Aside from being reflective of the day-to-day experience of individuals with diabetes [2], evidence has recently come to light indicating that TIR itself can predict the future risk of diabetes complications [3, 4]. For instance, retrospective analysis of CGM data collected over three consecutive days from 3262 individuals with type 2 diabetes revealed a significant inverse association of TIR with all stages of retinopathy after adjusting for age, sex, BMI, diabetes duration, blood pressure, lipids and HbA_{1c} [4]. Data associating TIR with a reduced risk of complications has also recently been reported for participants in the DCCT. During the course of that study, participants conducted seven-point profile testing of blood glucose concentrations for 1 day every 3 months. Although not computed with the aid of a CGM device, investigators derived TIR from the seven-point profiles and discerned that for every 10% lowering of TIR the adjusted hazard rate for the retinopathy outcome in the DCCT was increased by 64% (95% CI 51, 78) and the adjusted hazard rate for the microalbuminuria outcome was increased by 40% (95% CI 25, 56) [3]. This evidence is important because it begins to build the case that CGM metrics could be considered acceptable endpoints for clinical trials and accordingly used to inform regulatory decisions in the future [3, 23].

The relationship between TIR and hyperglycaemia

It is perhaps unsurprising that TIR appears to predict the risk of long-term diabetes complications, at least with respect to certain classical 'microvascular' complications, when one considers that TIR is largely determined by the extent and magnitude of hyperglycaemia. Although it is reported as the duration of time spent within a given range of glucose levels, with a target range of 3.9–10.0 mmol/l, the time spent with glucose levels that fall outside of this range is decidedly asymmetrical [24]. In other words, there is much more opportunity for glucose levels to sit above the target range before acute complications that demand urgent intervention may develop. For example, if an individual has a TIR of 60% (reflecting a mean of 14 h and 24 min in the target range) and even a relatively high TBR of 8% (1 h and 55 min below the target range), then TAR will be 32%. Thus, for 80% [32/(100 − 60)] of the time that this individual's glucose levels fall outside of the target range, they are likely to be above the upper limit of the target range (Fig. 1) [25]. As such, the mean TIR achieved in clinical trials inversely correlates with the mean achieved HbA_{1c}. For instance, in one report investigators compared paired HbA_{1c} and TIR data derived from 18 different research articles, observing a highly correlative inverse linear relationship between the two parameters ($r = -0.84$, $r^2 = 0.71$) (Fig. 2) [26]. Likewise, another recent study reported a similarly high inverse correlation between HbA_{1c} levels and TIR ($r = -0.75$) when comparing clinical trial end-of-study HbA_{1c} levels with at least 2 weeks of CGM data from 530 individuals with type 1 diabetes or insulin-treated type 2 diabetes [27].

The importance of including TBR in discussions on TIR

Given the relative insensitivity of TIR to hypoglycaemia it is important to include an indicator of the extent and severity of hypoglycaemia (i.e. TBR) when discussing TIR. The benefit of combining indicators of hyperglycaemia and hypoglycaemia in a metric of glycaemic control has gained increasing traction recently [28], with the utility of combining TIR with an indicator of the amount of time spent in hypoglycaemia being first emphasised during a point–counterpoint debate in 2015 [29]. CGM software can readily represent TIR along with TAR and TBR (with the percentage time in level 1 and level 2 for each) in the form of a 'stacked bar' [30], which is a helpful visual aid that can facilitate discussions between patients and healthcare professionals at clinic visits. Such a stacked bar can be visualised alongside the standardised 24 h ambulatory glucose profile (AGP) [31] licensed by most companies employing CGM software (Fig. 3).

Consensus recommendations on TIR

Recommendations from an international consensus on TIR recently set out guidance on targets for TIR, TBR and TAR [17] (summarised in Table 1). Briefly, there is currently insufficient evidence to justify separate targets for individuals with type 1 and type 2 diabetes and, for most people with diabetes, a TIR >70%, with a TBR <3.9 mmol/l of <4% and a TBR <3.0 mmol/l of <1% are recommended as targets [17]. The consensus stresses, however, that targets should be

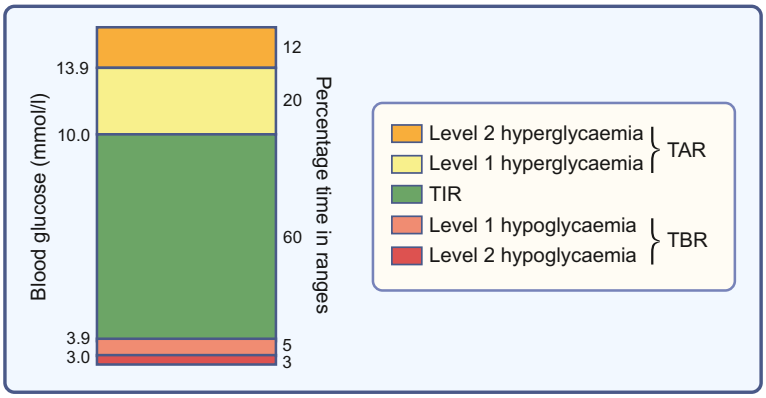

Fig. 1 Stacked bar representation of time in ranges. The stacked bar graph enables easy appreciation of TIR and frequency and severity (level 1 or level 2) of hypoglycaemia (TBR) and hyperglycaemia (TAR). In this example, the individual has a TIR of 60% with a relatively high frequency of hypoglycaemia at 8% (~1 h 55 min/day). Thus, in the example, when glucose falls outside of the target range, it is below range on 8% of occasions and, therefore, above range on 32% of occasions (i.e. 80% [32/(100 − 60)] of measurements that are outside the target range are above target). The example illustrates that, in isolation, TIR is largely determined by hyperglycaemia and, therefore, when it is considered, TIR needs to be considered together with a report of the extent and severity of hypoglycaemia. This figure is available as part of a downloadable slideset

individualised and it emphasises that each 5% increase in TIR is associated with clinically meaningful benefits [17]. Looser targets with more emphasis on decreasing TBR are recommended for older people or individuals at high risk of hypoglycaemia (Table 1) [17] and separate targets, with lower TIR thresholds, are recommended for pregnancy in type 1 diabetes (Table 1). Evidence is currently lacking as to achievable targets in pregnancy in type 2 diabetes or gestational diabetes [17].

Evidence underlying consensus recommendations on TIR targets

The objective of the international consensus on TIR was to develop targets that could provide guidance in interpreting CGM data in clinical care and in research [17]. The recommendations are timely and needed, given the rise in CGM use and the interest in the TIR metric, but they should be considered in the context of the evolving evidence and its current gaps.

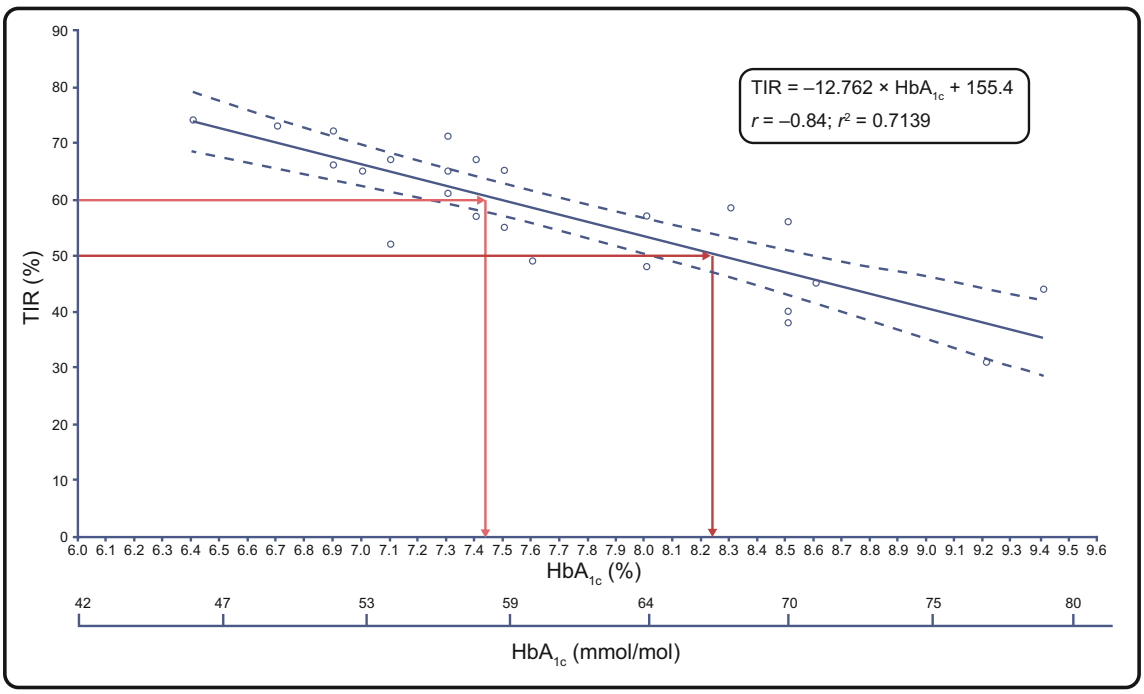

Fig. 2 The relationship between HbA_{1c} and per cent TIR derived using paired HbA_{1c} and TIR data from various clinical trials. The solid line is the best fit and the dashed lines represent the 95% CI. A 10% change in the TIR per cent (between 50% and 60%) correlates to a 9 mmol/mol (0.78%) change in HbA_{1c}. Adapted and reprinted from [26], with permission; the publisher for this copyrighted material is Mary Ann Liebert, Inc. publishers. This figure is available as part of a downloadable slideset

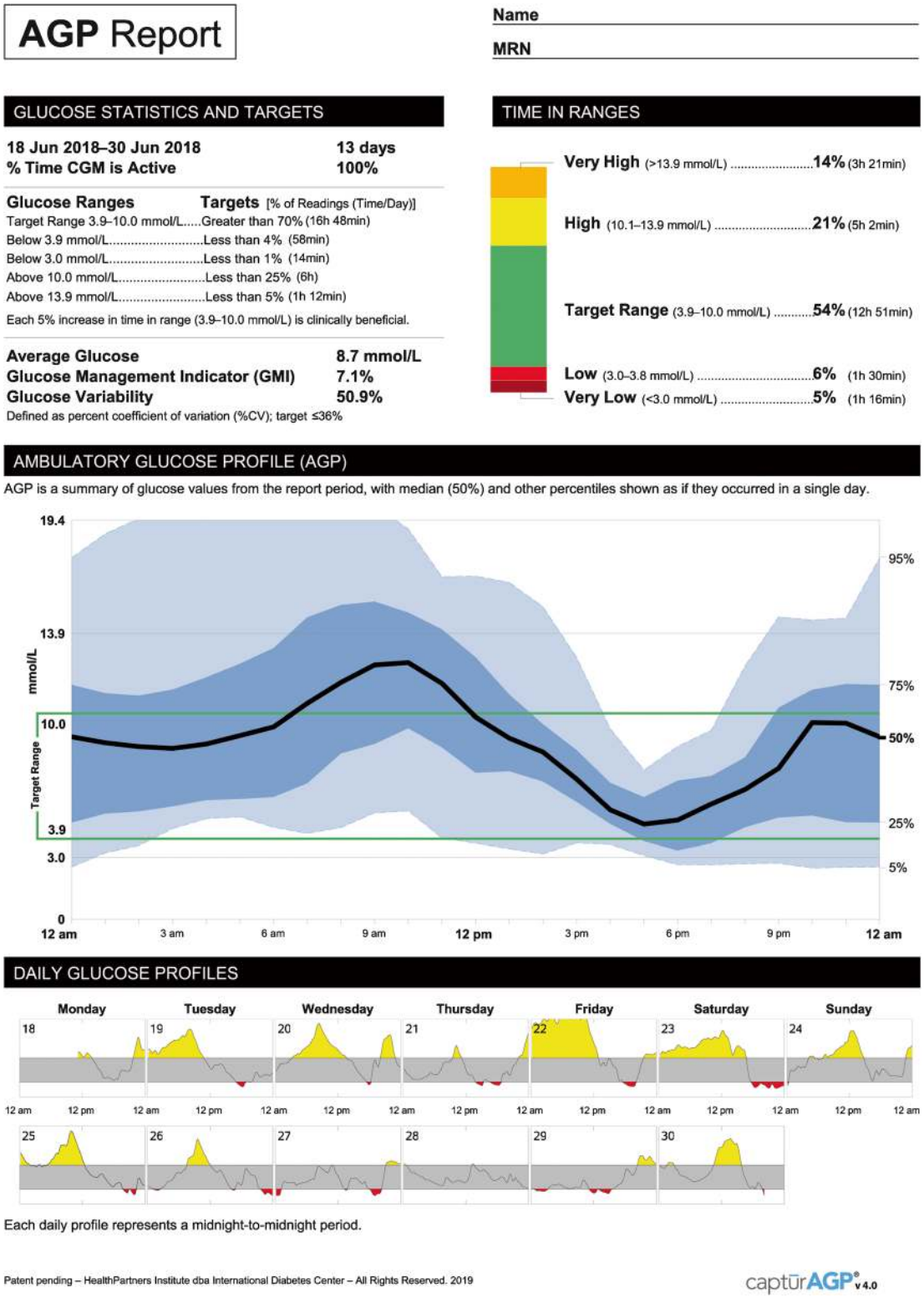

Fig. 3 Ambulatory glucose profile showing time in ranges as a stacked bar in the top right corner. © 2019 International Diabetes Center at Park Nicollet, Minneapolis, MN. Used with permission. See AGPreport.org for more information. This figure is available as part of a downloadable slideset

Type 1 diabetes Aside from the pregnancy setting [5, 6], or the initial studies associating TIR and complications risk [3, 4], most of the evidence supporting TIR target recommendations is based on TIRs achieved in clinical trials and the correlation between TIR and HbA_{1c} levels. In CGM research studies, mean TIRs have ranged between 51% for participants using

Table 1 Summary of guidance for assessment of glycaemic control using time in ranges from the international consensus on TIR

Diabetes group	TIR			TBR			TAR		
	Glucose target range (mmol/l)	Percentage readings within target range	TIR/day	Glucose (mmol/l)	Percentage readings below target range	TBR/day	Glucose (mmol/l)	Percentage readings above target range	TAR/day
T1D[a]/T2D	3.9–10.0	>70	>16 h 48 min	<3.9 <3.0	<4 <1	<1 h <15 min	>10.0 >13.9	<25 <5	<6 h <1 h 12 min
Older/high-risk[b] T1D/T2D	3.9–10.0	>50	>12 h	<3.9	<1	<15 min	>13.9	<10	<2 h 24 min
Pregnancy									
T1D	3.5–7.8	>70	16 h 48 min	<3.5 <3.0	<4 <1	<1 h <15 min	>7.8	<25	<6 h
T2D/GDM[c]	3.5–7.8	–	–	<3.5 <3.0	– –	– –	>7.8	–	–

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[a] For individuals aged <25 years, if the HbA_{1c} target is <58 mmol/mol (7.5%), TIR target is ~60%

[b] High-risk individuals include those with complications or comorbidities (e.g. cognitive deficits, kidney disease, joint disease, osteoporosis, fracture or cardiovascular disease)

[c] Data to inform targets for pregnancy in type 2 diabetes or GDM are currently lacking

GDM, gestational diabetes mellitus; T1D, type 1 diabetes; T2D, type 2 diabetes

CGM and multiple daily injections in the Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes (DIAMOND) trial [32] to approximately 70% among individuals using hybrid closed-loop technology [33–35]. In the study collating data from 18 previous research reports, a TIR of approximately 65% equated to an HbA_{1c} of 53 mmol/mol (7.0%) and an absolute change in TIR of 10% was associated with a change in HbA_{1c} of ~9 mmol/mol (0.8%) [26]. There is though quite a degree of variability in the reported relationship between TIR and HbA_{1c} according to different studies. For instance, in a separate report that analysed CGM data from four randomised trials encompassing 545 adults with type 1 diabetes, a 10% absolute change in TIR was, on average, associated with a ~7 mmol/mol change in HbA_{1c} [36]. However, the investigators emphasised that whereas TIR and mean glucose were highly correlated, a wide range of HbA_{1c} values were associated with any particular TIR [36]. By way of illustration, among participants who had worn a CGM device for 6 months, whereas a TIR of 60% equated to an estimated HbA_{1c} of 55 mmol/mol (7.2%), the 95% CI for the predicted value ranged between 45 mmol/mol (6.3%) and 66 mmol/mol (8.2%) (Fig. 4) [36]. Overall though, in that report an HbA_{1c} of 7.0% was approximately equivalent to a TIR of 70% [36]. In a separate study of paediatric participants, in which rtCGM or isCGM data were analysed over a period of 60 days, mean HbA_{1c} was 54 mmol/mol (7.1%) and mean TIR was 60.8% [37]. Finally, in the data from the DCCT in which TIR was derived from seven-point profiles, a notably lower TIR was associated with achieved mean HbA_{1c} values than that seen in CGM studies; the mean TIR in the conventional therapy group was 31% (mean HbA_{1c} 76 mmol/mol [9.1%]) and the mean TIR in the intensive treatment group was 52% (mean HbA_{1c} 56 mmol/mol [7.3%]) [3]. In sum, although there is currently a lack of trial-derived consensus for any specific TIR target across populations, in adults a TIR of 65–70%, derived by CGM, appears to equate with mean glucose levels broadly similar to those reflected by an HbA_{1c} of 53 mmol/mol (7.0%).

With respect to TBR targets, in the Glycaemic Control & Optimisation of Life quality in Type 1 Diabetes (GOLD) trial that compared CGM with SMBG in individuals with type 1 diabetes who used multiple daily injections of insulin [38], the TBR <3.9 mmol/l was 2.79% with CGM and 4.79% with SMBG, and TBR <3.0 mmol/l was 0.79% with CGM and 1.89% with SMBG [39]. In a retrospective analysis of data from individuals using hybrid closed-loop technology (Medtronic MiniMed 670G System), the TBR <3.9 mmol/l was 2.1% when using closed-loop Auto Mode [35]. Thus, whereas goals should be tailored to the individual, reasonable ranges for most people with diabetes approximate a TBR <3.9 mmol/l of <4% with a TBR <3.0 mmol/l of <1%.

Type 2 diabetes Existing data on achieved TIR in clinical trials of individuals with type 2 diabetes appear to be broadly comparable with those seen in type 1 diabetes populations. For example, in the Randomised Controlled Study to Evaluate the Impact of Novel Glucose Sensing Technology on HbA_{1c} in Type 2 Diabetes (REPLACE) study, participants with open access to isCGM data had a mean TIR of 14.1 h (~59%) with a TBR <3.9 mmol/l of 0.7 h (~3%) [40]. In the DIAMOND study, which examined Dexcom CGM use in participants with either type 1 or

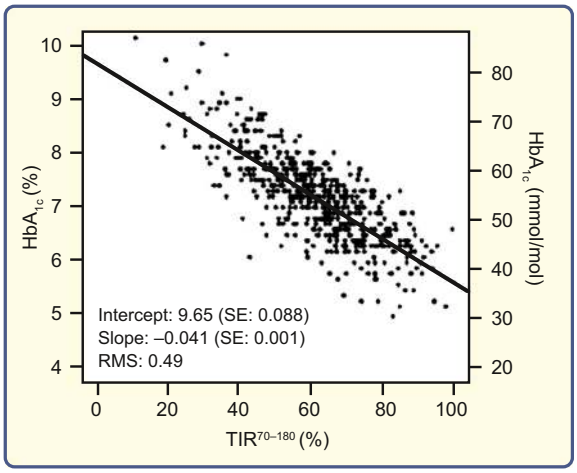

Fig. 4 Variability in the relationship between TIR and HbA_{1c}. The graph illustrates that whereas there is an inverse linear relationship between TIR and HbA_{1c}, a wide range of HbA_{1c} values may equate with any given TIR. Adapted from [36], with permission from SAGE publications. RMS, root mean square error; SE, standard error; $TIR^{70–180}$ = TIR 70–180 mg/dl (3.9–10.0 mmol/l). This figure is available as part of a downloadable slideset

type 2 diabetes, among individuals with type 2 diabetes, mean TIR after 24 weeks was 882 min (~61%) and mean TBR <3.9 mmol/l was 4 min (~0.3%) [12]. In this study, even baseline TBR was low, averaging 11–12 min per day (~0.8%) [12].

Pregnancy The amount of time spent in euglycaemia increases with advancing gestational age and differs between women with type 1 and type 2 diabetes [41]. In the Continuous Glucose Monitoring in Women With Type 1 Diabetes in Pregnancy Trial (CONCEPTT), mean third-trimester TIR (3.5–7.8 mmol/l glucose) for women wearing CGM was 68%, without an increase in TBR <3.5 mmol/l (3%) [5]. In a separate study from Sweden, mean third-trimester TIR (3.5–7.8 mmol/l glucose) was ~60% and TBR <3.5 mmol/l was ~7% [6]. Evidence from both studies indicates that for every ~5% reduction in TIR and 5% increase in TAR in the second and third trimesters, there is an increased risk of large for gestational age infants and adverse neonatal composite outcomes [5, 6, 42]. Because women with type 2 diabetes spend significantly less time in hyperglycaemia during pregnancy than women with type 1 diabetes, data are needed before guidance can be provided on achievable TIR, TAR and TBR targets for type 2 diabetes and gestational diabetes [17].

Positioning TIR in diabetes care

Given that TIR reflects mean glucose over time [36], where then should healthcare professionals position TIR relative to conventional markers of glycaemic control (e.g. HbA_{1c})? TIR is not a replacement for measurement of HbA_{1c} levels, rather it provides complementary information as to the quality of overall glucose control. For instance, whereas HbA_{1c} typically reflects glucose levels over the preceding 8–12 weeks, TIR can be measured over shorter periods of time; TIR reflects continuous glucose levels over that period of time and it can be responsive to acute fluctuations [18]. As such, TIR has been identified by individuals with diabetes as impacting the quality of daily life [2] and it may therefore correlate better with the patient experience and patient-reported outcomes (PROs) [18]. Furthermore, discussions on TIR provide an opportunity to consider mean glucose levels in the context of the severity and amount of hypoglycaemia (i.e. TBR). There is also increasing evidence linking increments in TIR to improved outcomes in pregnancy [42]. In addition, TIR may be useful at times when there is discordance between HbA_{1c} levels and mean glucose (e.g. chronic kidney disease or haemoglobinopathy). However, specific data in these populations are currently lacking and other approaches to reconciling discordances between HbA_{1c} and mean glucose also exist that do not require CGM wear (e.g. measurement of fructosamine or glycated albumin or normalisation of HbA_{1c} for mean red blood cell age [M_{RBC}]) [43–45]. Likewise, other CGM metrics (e.g. GMI) may be equally as effective as TIR in individualising glycaemic targets in such circumstances. Finally, glycaemic variability can be a major barrier to the optimisation of glucose control [46] and, although the strength of association is somewhat controversial, it has also been linked to complications risk [29, 47, 48]. When considering glycaemic variability, %CV is a better indicator, with a %CV ≤36% considered indicative of stable glucose levels [11, 17, 49].

Barriers to the widespread adoption of time in ranges as primary metrics of glucose control

Evidently, the major barrier to the widespread adoption of time in ranges as the primary means by which the quality of glucose control is represented is that the majority of people living with diabetes do not use CGM technology. The global CGM market is estimated at over US$ 1 billion and has been forecast to exceed US$ 4 billion by 2024 [50]. Nonetheless, there will continue to be many people with diabetes who, through choice or otherwise, will not make use of or have access to CGM technology in the future. For instance, even among T1D Exchange registrants up to 2018, 60–70% of individuals were not using CGM [8]. In a subpopulation of 1503 adult T1D Exchange participants, investigators surveyed barriers to device uptake [51]. Among these

barriers, insurance coverage and cost of devices and supplies were cited as barriers by over 50% of respondents [51]. Among the barriers that were considered by the investigators to be modifiable, 'hassle of wearing devices all of the time' (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) were the most commonly endorsed reasons for choosing not to wear a device [51]. Hopefully, continuing technological advances such as smaller devices, more affordable devices or implantable devices will be able to circumvent some of these obstacles in the coming years. Reactions to device adhesives can be troublesome for some individuals too and their importance has tended to be overlooked in the past [52–54]. Work also needs to be done to improve the acceptability of CGM devices for continuous wear, especially in certain groups including the emerging adult population who currently have the lowest uptake rates of CGM technology [51]. Likewise, work needs to be done to bridge the racial and income disparities that exist in CGM use [8]. Sensor accuracy, although improved, remains imperfect particularly at extremes of sensor glucose levels (hypoglycaemia or hyperglycaemia) or when the rate of change is especially rapid [55]. This may have particular bearing on discussions around TBR. The most commonly used metric of sensor accuracy is the mean absolute relative difference (MARD) between sensor readings and reference blood glucose values, with an arbitrarily assigned MARD of under 10% generally being considered acceptable for insulin dose decision-making [56]. Because MARD can be affected by a number of variables, including the reference system, the number of paired readings and overall study design [55], it is generally unwise to compare manufacturer-reported MARDs between devices. However, in one small study mimicking real life conditions, investigators evaluated the accuracy of the Freestyle Libre (Abbott), Dexcom G4 Platinum (Dexcom) and Medtronic Minimed 640G (Medtronic) CGM devices when used simultaneously, observing diminished accuracy of each device in the hypoglycaemic range (overall MARDs of 13.2%, 16.8% and 21.4%, respectively; MARDs in hypoglycaemia [<3.9 mmol/l glucose] of 14.6%, 23.8% and 26.9%, respectively) [57].

Future directions

Despite the potential added utility of including discussions of time in ranges in diabetes care clinical encounters, a number of questions remain unanswered. Currently, the evidence linking reduced TIR to increased risk of diabetes vascular complications is still rather limited, being restricted to the imputation of TIR from seven-point profiles or retrospective CGM data collected over 3 days [3, 4]. Many people using CGM devices wear their devices continually and the benefits of CGM increase with the frequency of wear [58]. Although the derivation of CGM metrics over a 14 day period is recommended [17], the optimal time period over which TIR should be determined for predicting complications risk is currently unknown. Conversely, many other people wear their CGM device intermittently and it is unclear whether any differences exist in the clinical utility of TIR during intermittent vs continuous CGM wear. A number of other indicators of glucose control are also available, such as the comprehensive glucose pentagon (CGP) [59], haemoglobin glycation index [60, 61], glycaemic variability percentage (GVP) [62], other indicators of glycaemic variability [29], or more complex composite risk indices [63]. However, whether the advantages in comprehensiveness of such approaches outweigh the limitations in terms of their accessibility to individuals living with diabetes remains to be seen. Similarly, at the present time, neither TIR nor any of these other alternative metrics has demonstrated themselves to be substantially more effective at predicting complications risk than HbA_{1c} alone. More broadly, with its comparative affordability, factory calibration and 14 day wear, isCGM has opened up CGM opportunities for broader populations, with the Freestyle Libre already being used by over 1 million individuals [64]. It should be recognised that, at the current time, recommendations of TIR thresholds and targets have been assumed to be the same regardless of the CGM device being used, although there is a general dearth in head-to-head comparisons (e.g. isCGM vs rtCGM). Furthermore, work is needed to better understand the potential positioning of time in ranges in type 2 diabetes management and to define achievable TIR and TBR targets in type 2 diabetes in pregnancy and gestational diabetes. Likewise, and analogous to the concept of linking HbA_{1c} goals to the risk of iatrogenic hypoglycaemia elegantly laid out by Cryer [28], in the future we may be better equipped to recommend individualised TIR thresholds and targets for individuals with diabetes. These thresholds and targets could be tailored to both the type of diabetes and the risk of iatrogenic hypoglycaemia according to drug therapy.

Summary

In summary, among the host of possible metrics now available to patients and healthcare professionals making use of CGM technology, TIR has emerged as an intuitive metric that may correlate better with PROs and that itself is associated with the risk of long-term complications. However, when engaged in discussions of TIR it is imperative that healthcare professionals include an indicator of hypoglycaemia and its severity in the conversation (i.e. TBR <3.9 mmol/l and TBR <3.0 mmol/l). Based on current evidence, a TIR of >70% would appear to be a reasonable target for most individuals,

Summary

- TIR is a key metric of the quality of glucose control
- Evidence is beginning to emerge linking lower TIR to increased risk of long-term diabetes complications and adverse pregnancy outcomes
- TIR correlates inversely with HbA_{1c} and is largely indicative of the extent and magnitude of hyperglycaemia
- Discussions on TIR should include discussions on TBR
- Recent consensus recommendations suggest targets of TIR >70%, with TBR (<3.9 mmol/l) <4% and TBR (<3.0 mmol/l) <1% for most individuals with type 1 or type 2 diabetes, although targets should be individualised
- Different targets should be considered for older or high-risk individuals, paediatric populations and pregnant women

roughly equating to an HbA_{1c} of ≤53 mmol/mol (7.0%), if it can be achieved with a TBR <3.9 mmol/l of <4% and a TBR <3.0 mmol/l of <1%. As is always the case, though, glycaemic goals should be individualised and rarely does a better opportunity present itself to individualise treatment goals than with the personal use of CGM in diabetes self-management.

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