

Time in range centered diabetes care

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Abstract. Optimal glycaemic control remains challenging and elusive for many people with diabetes. With the comprehensive clinical evidence on safety and efficiency in large populations, and with broader reimbursement, the adoption of continuous glucose monitoring (CGM) is rapidly increasing. Standardized visual reporting and interpretation of CGM data and clear and understandable clinical targets will help professionals and individuals with diabetes use diabetes technology more efficiently, and finally improve long-term outcomes with less everyday disease burden. For the majority of people with type 1 or type 2 diabetes, time in range (between 70 and 180 mg/dL, or 3.9 and 10 mmol/L) target of more than 70% is recommended, with each incremental increase of 5% towards this target being clinically meaningful. At the same time, the goal is to minimize glycaemic excursions: a recommended target for a time below range (< 70 mg/dL or < 3.9 mmol/L) is less than 4%, and time above range (> 180 mg/dL or 10 mmol/L) less than 25%, with less stringent goals for older individuals or those at increased risk. These targets should be individualized: the personal use of CGM with the standardized data presentation provides all necessary means to accurately tailor diabetes management to the needs of each individual with diabetes.

Key words: time in range, glucose variability, continuous glucose monitoring, diabetes technology, closed-loop, self-monitoring of blood glucose, diabetes mellitus

Introduction

Diabetes has an increasing worldwide prevalence over the past decades from 151 million in 2000 to estimated 463 million (9.3% of all adults aged 20–79 yr) in 2020, and an additional 1.1 million children and adolescents with type 1 diabetes (1). Living with diabetes is challenging for individuals with this chronic condition as well as for those taking care of them. The lifelong goal of diabetes care is maintaining glucose levels as close to normal as possible and as early as possible in the course of the disease, thus delaying or possibly preventing devastating long-term diabetes complications (2–5).

Optimal diabetes management should be multidisciplinary and tailored for each person with diabetes (PWD), and is dependent on regular glucose monitoring, precise insulin dosing, and rational decision-making support. However, everyday diabetes care is complicated by the variability in insulin requirements for each PWD as insulin dose needed to maintain normoglycemia fluctuates from one day (or night) to another, and might be, especially in children and

adolescents, challenging to achieve with conventional treatment modalities (6, 7).

In the past decades, glucose management was primarily assessed with the glycated hemoglobin A1c (HbA1c), an evidence-based and broadly-accepted surrogate outcome measure for evaluating the efficacy of diabetes care in routine clinical practice and in numerous clinical trials (including Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study of the DCCT cohort), and was recognized as a reliable and indirect biomarker that reflects long-term average glucose control (2–5, 8). Current international guidelines recommend that HbA1c for the majority of children and nonpregnant adults should be below 53 mmol/mol (7%) or even below 47.5 mmol/mol (6.5%) if this can be achieved safely (9, 10).

While HbA1c realistically captures the average glycaemic control in the retrospect, it is limited in assessing short-term outcomes and day-to-day glucose fluctuations (11, 12). There is substantial evidence that these glucose excursions »beyond HbA1c« are

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associated with the damage to susceptible organs or/and chromosomes, likely through oxidative stress (13–15), and were highlighted as significant risk factors for cognitive function and evolving brain structures early in the disease course, especially in young children with type 1 diabetes (16–18). Additionally, HbA1c lacks the information about acute complications, such as severe hypoglycemia or diabetic ketoacidosis that are, together with the fear of hypoglycemia, important barriers towards diabetes care optimization. Moreover, acute complications cause stress and anxiety, increase treatment costs, and decrease the quality of life (QoL) and psychological well-being of the youth with diabetes and their families (12, 19, 20).

Continuous glucose monitoring (CGM), either real-time (rtCGM) or intermittently scanned (isCGM), effectively addresses these barriers: data derived from CGM present a more comprehensive glucose control picture than HbA1c alone (21). CGM devices provide a broad spectrum of additional glucose management metrics, including proportions of time in range (TIR), time below range (TBR), time above range (TAR), and glucose variability (GV), that are at hand to PWDs and their health-care providers (HCPs) for individualizing the diabetes management and for making real-time treatment modifications.

From Intermittent to Continuous Glucose Monitoring

Regular glucose monitoring allows PWDs to guide their insulin therapy and assess whether their glucose targets are safely achieved. Frequent self-monitoring of blood glucose (SMBG) from capillary blood has considerably improved glycemic control by giving users the capacity to self-manage and individually tailor insulin dosing, and is considered a fundamental component of effective diabetes treatment and daily management of PWDs on insulin therapy (22).

SMBG has several limitations as blood is sampled intermittently, pinpointing only fragments of real glucose fluctuations, thus failing to reveal ongoing glucose excursions even if performed frequently. Episodes of asymptomatic hypoglycemia and also hyperglycemia could therefore be overlooked and not incorporated into decision-making. Additionally, a recent study demonstrated that many glucometers for personal use previously cleared by authorities in real life do not meet the level of accuracy currently required for regulatory clearance (23).

SMBG is throughout the world being replaced with CGM as the glucose monitoring of choice for insulin dosing; this replacement is based on a considerable body of evidence generated over the past 15 years. Contrary to SMBG, CGM provides an almost continuous string of glucose concentration measurements (every 1–5 min). CGM devices generally consist of a disposable on-body sensor that measures glucose concentration in the interstitial fluid, and a transmitter that broadcasts

the sensor values (usually in 5–15 min intervals) to a dedicated receiver and/or other portable devices (e.g. smartphone, smart-watch, tablet). Data can be seen in real-time (rtCGM), stored in the cloud and shared with other family members. The CGM sensor values usually closely correlate with blood glucose concentration when glucose is stable, with a mean time lag of 5 min or less; during episodes of rapid glucose changes like post-simple-carbohydrate meal or exercise, however, the time lag can exceed 10 minutes (24). isCGM is a variety of CGM that presents glucose concentration only on demand (25, 26) but with recently enabled alarms it is coming closer to rtCGMs.

The only currently approved implantable CGM system has a sensor that is fully implanted under the skin by a healthcare provider, and functions for 90–180 days with data visualization through an on-body device (27).

Following the first major randomized controlled trial (RCT) with CGM use funded by JDRF (28), numerous RCTs confirmed efficacy and safety of CGM devices in both people affected with type 1 and type 2 diabetes (29–35), including individuals with severe hypoglycemia and/or hypoglycemia unawareness (36–39), on multiple daily injections (MDI) therapy (40), and particularly during pregnancy complicated by type 1 diabetes (41). Importantly, these positive outcomes were associated with a projected yearly reduction in diabetes-related cost worth several million USD (42). Additionally, user satisfaction and consequently mean sensor usage was significantly higher, including significant improvement of QoL measures (43).

The use of CGMs has been endorsed by the American Diabetes Association (ADA) in its 2020 Standards of Medical Care in Diabetes (33) the American Association of Clinical Endocrinologists (AAACE) (44, 45), the International Society for Pediatric and Adolescent Diabetes (ISPAD) (46), and the Endocrine Society (47). The use of CGM is globally increasing exponentially in all age groups. Recent data from the T1D Exchange Registry reported that about 30% of participants have been using CGM in the period from 2016 to 2018 compared to 7% in 2010 to 2012 (48). Similarly, the most recent DPV Registry reported extensive CGM use in the majority of children with type 1 diabetes aged below 10 yr and overall usage in 38% of individuals with type 1 diabetes (49). This significant increase is likely related to the approval of isCGM and rtCGM systems for non-adjunctive use, better accuracy and reliability of CGM devices, as well as broader reimbursement policy, some with demonstrated cost-effectiveness (50, 51).

Real-world efficacy data are in line with observations from RTCs: in a European registry, the CGM use was associated with better mean glucose and less hypoglycemia (52), in the T1D Exchange Registry, CGM usage was associated with lower HbA1c (48), and similarly in the DPV Registry CGM initiation lowered HbA1c and reduced risk for both SH and DKA (53). Recently, in the largest real-world data set including

more than 10,000 individuals with type 1 diabetes from the UK, isCGM use improved glycemic control, especially in those with a higher baseline HbA1c, improved hypoglycemic awareness, reduced diabetes-related distress, and reduced hospital admissions (54). A recent head-to-head comparison between rtCGM and isCGM demonstrated potential advantages of the former, which may influence further development of CGM devices (55).

Standardized Data Reporting Interpretation

CGM data can be accessed in real-time on personal devices and curated personal data can be viewed using software packages. The data analysis tools offer PWDs and HCPs a wide range of metrics of glucose control quality, including proportion of sensor use, mean glucose, glucose management indicator (GMI; previously “estimated HbA1c”), glycemic variability (coefficient of variation – CV) and time in ranges – TIR, TBR and TAR (21, 56). 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. However, until recently, these metrics were reported in various ways and ranges were defined diversely, therefore, it was almost impossible to compare results from one report to another.

In 2017, an international consensus recommended standardized CGM reporting and defined outcomes definitions with a core set of ten CGM metrics for reports (21). Definitions of the minimum requirements for CGM performance, such as meeting ISO (International Organization for Standardization) standards, the relationship of dependence of CGM calibration with glucometers (non-adjunctive us), and an acceptable CGM accuracy, defined as an absolute relative difference (MARD), were agreed upon. For reliable data assessment, studies have demonstrated that 10–14 d of CGM data generally provide a good approximation of 3 months of glucose data (57).

It is imperative that all CGM users should be trained in how to access, interpret, and answer questions regarding their glycemic control with accessible devices and tools.

Decision Making and Time in Range Targets

To make CGM data clinically meaningful for routine day-to-day diabetes management, clear guidance on CGM-derived glycemic targets should be provided to both PWDs and HCPs.

Recently, several major international societies formally endorsed an international consensus report on clinical targets for CGM data (58); notably, the consensus participants included also individuals with diabetes outside the medical profession.

The consensus suggested easy to understand TIR targets, along with TBR and TAR targets for routine

management of type 1 and type 2 diabetes (Table 1). The reporting, presentation and visualization of CGM data should smoothen the communication between PWDs and HCPs, particularly when a standardized report (eg. Ambulatory Glucose Profile - AGP (59)) displays the key CGM metrics, including proportions of glucose values in different ranges over a specified time period, the recommended target for each CGM data range, and a visual demonstration of the CGM values distribution according to the time of day.

The principal goal for all children and adults with type 1 diabetes and type 2 diabetes is to maintain:

- At least 70% ((16 h and 48 min per d) of TIR (70–180 mg/dL / 3.9–10 mmol/L),
- while at the same time minimizing both TBR and TAR:
- less than 4% (1 h per d) of TBR (< 70 mg/dL / 3.9 mmol/L) and
- less than 25% (6 h per d) of TAR (> 180 mg/dL / 10 mmol/L).

Targets should be individualized and in line with personal needs and circumstances. Each incremental 5% improvement in TIR is associated with clinically significant benefit.

While for pregnancy complicated with diabetes recommended targets remain the same, TIR is defined tighter (63–140 mg/dL) as glucose levels are physiologically lower during pregnancy (60).

A relevant improvement in diabetes care with the use of the new metrics is only possible through its broad understanding and adoption by PWDs and HCPs. It is therefore important to demonstrate that TIR metrics relate to and predict clinical outcomes so that we can together finally improve long-term diabetes outcomes with less day-to-day disease burden.

Because TIR can be evaluated on a near-hourly basis, it provides an important advantage over HbA1c: interpreting glycemic control in terms of TIR offers a more nuanced, cause-and-effect related understanding of glucose fluctuations. One can recognize behaviours and decisions that drive glucose levels out-of-range and prospectively find where/when changes can be made. From PWDs perspective, TIR is more accessible and at the same time more intuitive. For example, in one survey of 3461 PWDs, TIR emerged as the top outcome measure considered to have a ‘big impact’ on daily life with diabetes that both reflects PWDs’ priorities and can be used to quantitatively evaluate treatment efficacy (12).

To show the correlation between HbA1c and TIR, Vigersky and McMahon analyzed data from 18 studies including 2577 PWD and found a strong relationship between TIR and HbA1c ($R = -0.84$; $R^2 = 0.71$) (60). Their results showed that for every 10% change in TIR, there was a 0.8% change in HbA1c.

Similar relationships were observed by Hirsch and colleagues who analyzed individual-level data from four randomized trials including 545 PWDs who had central laboratory measurements of HbA1c. TIR of 70% and 50% strongly corresponded with an HbA1c of approximately 7% (53 mmol/mol) and 8% (64 mmol/mol), respectively.

Table 1. Targets for glycemic control: Type 1 / Type 2 and older / high-risk individuals

		Type 1 / Type 2	Older/high-risk Type 1 / Type 2
Time above range (TAR)	Above target range	> 180 mg/dL > 10.0 mmol/L	
	% of time/d	< 25% < 6 h	
	Above target range	> 250 mg/dL > 13.9 mmol/L	> 250 mg/dL > 13.9 mmol/L
	% of time/d	< 5% < 1 h, 12 min	< 10% < 2 h, 24 min
Time in range (TIR)	Target range	70–180 mg/dL 3.9–10.0 mmol/L	70–180 mg/dL 3.9–10.0 mmol/L
	% of time/d	> 70% > 16 h, 48 min	> 50% > 12 h
Time below range (TBR)	Below target range	< 70 mg/dL < 3.9 mmol/L	< 70 mg/dL < 3.9 mmol/L
	% of time/d	< 4% < 1 h	< 1% < 5 min
	Below target range	< 54 mg/dL < 3.0 mmol/L	
	% of time/d	< 1% < 15 min	

Each incremental 5% increase towards time in range (TIR) targets is associated with clinically significant benefits for Type 1 / Type 2. Adapted from: Battelino T, *et al.* Clinical targets for continuous glucose monitoring data interpretation: recommendations from the International Consensus on Time in Range (58).

An increase in TIR of 10% (2.4 h per day) decreased HbA1c for about 0.5% (5.0 mmol/mol) (61). Petersson and coworkers analyzed data from 133 children with type 1 diabetes from Sweden and demonstrated a significant non-linear relationship between time in tighter range 70–140 mg/dL and HbA1c ($R^2 = 0.69$) over 60 days in frequent CGM (at 80% of the time) users (62). Beck and coworkers (63) re-analyzed data from the DCCT study. They used 7-point blood glucose profiles to validate the use of TIR as an outcome measure for clinical trials and demonstrated that the hazard ratio for retinopathy progression increased by 64% for each 10% decrease in TIR. Similarly, the hazard ratio for microalbuminuria development increased by 40% for each 10% reduction in TIR. Lu and colleagues evaluated the association between the TIR, assessed by CGM, diabetic retinopathy as a marker of microvascular complications (64), and intima media thickness, as a marker of macrovascular complications (65), in individuals with type 2 diabetes. Individuals with more progressive retinopathy, regardless of stage, and with abnormal intima media thickness had significantly lower TIR, and a decreased risk for complications with improved TIR was demonstrated (64, 65). Recently, an association between higher TIR and reduction in the urinary creatinine-albumin ration was demonstrated from a prospective randomized controlled

trial (66). Several prospective clinical trials with TIR as the primary outcome are ongoing.

Finally, TIR can be used for evaluating the efficacy of different treatment modalities. Automated glucose-responsive insulin therapy (closed-loop) was revitalized (67) and a roadmap towards closing-the-loop in six steps was defined 15 yr ago (68, 69). Consequently, a broad spectrum of treatment modalities for closing the loop is currently available on the market (in details discussed elsewhere (70)), including low-glucose suspend (71, 72), predictive low-glucose suspend systems MiniMed 640G (*Medtronic Diabetes, USA*) and Tandem t:slim X2 Insulin Pump with Basal IQ®Technology (*Tandem Diabetes care, USA*) (73, 74) and automated insulin delivery systems Medtronic MiniMed 670G and 780G (*Medtronic Diabetes, USA*) (75), DBLG1 (*Diabeloop, France*) (76), Tandem Diabetes Care t:slim X2 with Control IQ (*Tandem Diabetes care, USA*) (77) and CamAPX FX (*CamDiab Ltd, UK*) (78).

The efficacy of newer technologies was evaluated in a recent network meta-analysis: closed-loop systems are demonstrated to have several advantages over other treatment modalities (79). **Figure 1** summarizes data regarding TIR from recent randomized controlled trials including individuals with type 1 diabetes using either closed-loop therapy, predictive low glucose suspend or

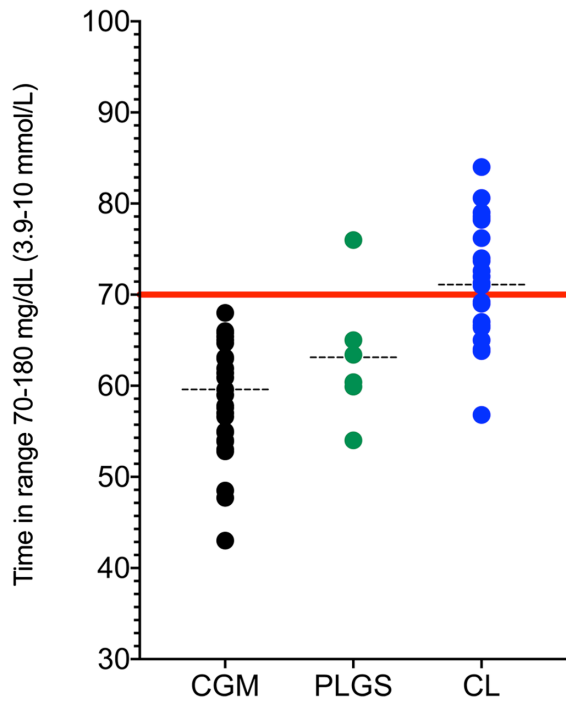


Fig. 1. Time in range for different treatment modalities from recent randomized controlled trials. CGM, Continuous Glucose Monitoring; PLGS, Predictive Low Glucose Suspend; CL, Closed-loop. Data from randomized controlled trials including children, adolescents and adults with type 1 diabetes for the last 5 years are included (34–36, 38, 39, 55, 73, 74, 77, 78, 80–116).

CGM alone.

Summary

In conclusion, with a proven benefit on glycemic

outcomes and QoL, CGM devices are being increasingly adopted worldwide. To unify and improve clinical outcomes and quality of life with our routine diabetes care, we need to constantly improve the presentation and usage of provided CGM data. Individual CGM daily glucose profiles within the AGP can be used as a standardized overview and can effectively guide shared decision-making between a user and her/his HCP to personalize diabetes care and enable real-time treatment adjustments. This communication can be facilitated with clear and understandable time in ranges targets. Based on existing data, current recommendations set time in range (70–180 mg/dL, or 3.9–10 mmol/L) of more than 70%, with time below range (< 70 mg/dL, or < 3.9 mmol/L) of less than 4% for the majority of people with type 1 or type 2 diabetes. Every 5% increment towards the time in range target is clinically meaningful. All treatment targets can be effective in practice only if personalized and agreed upon with each individual with diabetes.

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