Associations of Time in Range and Other Continuous Glucose Monitoring–Derived Metrics With Well-Being and Patient-Reported Outcomes: Overview and Trends

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Time in glucose ranges is increasingly relevant for research and clinical practice. Whereas the clinical validity of these metrics has been demonstrated with regard to long-term complications, their associations with patient-reported outcomes such as well-being, diabetes distress, and fear of hypoglycemia remain an open research question. This article reviews existing evidence on links between times in glycemic ranges and patient-reported outcomes. It also describes a novel research approach of using ecological momentary assessment to analyze on a more granular level in real time possible associations of these parameters of glycemic control and patient-reported outcomes. Such an approch could further our understanding of how glucose and patient-reported outcomes may be interconnected.

In the past, assessment of glycemic control was primarily based on A1C measurement (1–3) and self-monitoring of blood glucose (SMBG) (4,5). A1C as a measure of mean glucose levels over the past 8–12 weeks is a good predictor of long-term complications but fails to capture the day-to-day experiences of glucose management (6). This is particularly true regarding hypoglycemic exposure and glucose fluctuations. SMBG only provides spot measurements of glucose values, which leaves glycemic control between these measurements unrecognized (especially at night). These limitations of A1C can be addressed by continuous glucose monitoring (CGM) (1–3).

In the past few years, clinical practice has registered a widespread adoption of CGM. Registry data from the United States and Germany demonstrate that the use of CGM slowly increased from 3% in 2006 to ~6% in 2011 and then exponentially increased to nearly 40% in 2017–2018 (7,8). A recent survey among specialized diabetes centers in Germany showed that nearly 65–70% of people with type 1 diabetes use some kind of CGM device (9,10). The number of people with type 2 diabetes using CGM devices is also increasing, with an estimated proportion of 10–15% (9,10).

With the emergence of CGM in peoples' daily life came the introduction of new parameters of glycemic control such as time below range (TBR), time in range (TIR), time above range (TAR), glycemic variability, and subsequent statistics such as mean glucose, median glucose, glucose percentiles, and coefficient of variation (CV) (5). The introduction of these CGM-derived parameters sparked a debate about the limitations of A1C as the gold standard for measuring glycemic control (1–3) and whether these CGM-derived parameters should be considered superior (4,5). It has been demonstrated that lower (blood glucose-derived) TIR and higher TAR are strongly associated with an increased risk for retinopathy and microalbuminuria (11) and could also be indicative of cardiovascular disease (12,13). Furthermore, TBR and parameters of glycemic variability have shown clinical usefulness regarding risk assessment for severe hypoglycemic events (14–16). Thus, new consensus statements have now been published on how best to define and report these parameters and their clinical relevance (5,17). Now standing alongside A1C (17), these CGM-derived parameters of glycemic control have demonstrated their metabolic relevance.

However, the patient-reported, subjective relevance of these parameters remains an open research question because CGM and its derived parameters increasingly define peoples' daily diabetes management. Questions have arisen as

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to whether time spent in, above, and below target glycemic ranges is associated with patient well-being and other patient-reported outcomes (PROs) such as diabetes distress and fear of hypoglycemia and whether this possible association results from a direct physiological impact.

The relevance of analyzing associations between CGM-derived parameters and PROs is also emphasized by the U.S. Food and Drug Administration's call for systematic inclusion of the patient perspective in the evaluations of interventions (18) and the American Diabetes Association's statement that glycemic targets should "address the needs and preferences of each patient" (1).

To date, associations between CGM-derived parameters of glycemic control and PROs have not been consistently evaluated. Consequently, the recent consensus statements hardly mention and address PROs at all (5,17). There is promise in analyzing the association between these glycemic parameters and measures of PROs, as CGM is more reflective than A1C of real-time experiences (6,19) and could yield interesting insights into how glucose and psychosocial well-being affect each other.

To shed some light on the association between CGM-derived parameters of glycemic control and PROs, this narrative review has three aims. First, it summarizes current evidence on the association from interventional and observational studies. Second, it highlights ongoing studies that use ecological momentary assessment for a more real-time measurement of PROs to mirror real-time CGM-based assessment of glycemic control. Third, it offers a discussion of the implications for future research and clinical practice regarding CGM-derived parameters of glycemic control and their impact on well-being.

Evidence From Interventional Studies

CGM-derived glycemic parameters have been the target of many methodologically sound interventional studies evaluating diabetes technology such as CGM and automated insulin delivery (AID) systems. These interventional studies have shown large effects, with substantial improvements in TIR, TBR, TAR, and glycemic variability when using real-time CGM (rtCGM) (20–22) or AID (23–26) systems. If such improvements in TIR and other metrics are accompanied by improvements in PRO measures, this would suggest a direct association between CGM-derived parameters and well-being.

Overall, however, these large glycemic effects were rarely associated with improvements of the same magnitude in PROs (27,28). The DIAMOND trial (27) that evaluated the impact of rtCGM on glycemic control demonstrated significant reductions in glycemic variability, TBR, and TAR but found no changes in well-being, health status, or hypoglycemia fear. Only diabetes distress was significantly improved. Interestingly, satisfaction with the rtCGM system was not associated with changes in any of the parameters of glycemic control. The HypoDE study (28) showed an effect size of 1.43 SDs regarding the beneficial effect of rtCGM on TBR. This effect translated to significant improvements in fear of hypoglycemia and hypoglycemia-related distress but with markedly lower effect sizes of 0.32 and 0.41 SDs, respectively. Similar findings were observed in the IN CONTROL trial (29), which also showed significant improvement in TIR, TBR, TAR, and glycemic variability but only a specific effect on hypoglycemia worries; TIR improved by 2.0 SDs, whereas hypoglycemia worries only improved by 0.12 SD. These findings are corroborated by evidence from older populations with type 1 diabetes. The WISDM (Wireless Innovation for Seniors With Diabetes Mellitus) trial (30) demonstrated significant effects of rtCGM on all prespecified CGM-derived parameters but not a single significant improvement in any of the 15 PRO measures. Specifically, rtCGM was found to significantly reduce TBR by 27 minutes/day compared with SMBG, but hypoglycemia fear and diabetes distress remained unchanged.

Randomized controlled trials evaluating AID systems demonstrated significant improvements in TIR and other glycemic parameters, but concomitant improvements in PRO measures have not yet been reported (24–26). However, there is some evidence that the resulting improvement in TIR and other metrics from using AID systems is associated with a positive impact on the well-being of people with diabetes (31,32).

The interventional studies provide a first hint of the association of TIR and other parameters on well-being. Overall, these results indicate that improvements in TIR or other parameters do not necessarily lead to proportional improvements in well-being or a reduction of diabetes distress. However, isolated effects on specific aspects of well-being have been observed, such as the reduction of TBR and a subsequent improvement in hypoglycemia distress and fear in hypoglycemia-prone people with diabetes (28,29). Notably, suboptimal glycemic control is only one potential source of impaired well-being. Thus, improvements in glycemic control may not necessarily lead to improvements in, for example, overall diabetes distress because other challenges of living with diabetes may still be perceived as distressing. Further research is needed to analyze whether AID systems or closed-loop glycemic control may remove a greater portion of the burden of

diabetes management so that improvements in PRO measures become detectable.

Evidence From Observational Studies

To date, only few observational studies have directly investigated associations between CGM-derived glycemic parameters and PROs. The primary question arises as to whether these metrics play a significant role in people's everyday lives. In comparison with blood glucose measurements at single time points, CGM systems confront their users with dense information about past, current, and predicted future glucose levels. Qualitative research has shown that CGM use increases feelings of control and safety and fosters insights into daily glucose patterns (33). On the other hand, the amount of information and automated responses such as alarms can be demanding, and information overload is a likely barrier to the effective use of CGM in people's daily self-management (34). Despite the potentially challenging data complexity, CGM-derived parameters appear to be an important outcome for people with diabetes; in a 2017 online survey, Runge et al. (19) assessed which self-management factors have the greatest impact on the daily lives of people with type 1 or type 2 diabetes. Second only to food choices, participants rated TIR as a crucial factor, reflecting the perceived relevance of this parameter in everyday life. Furthermore, people with type 1 or type 2 diabetes using insulin reported that "blood glucose number on target all day" would contribute most to a "positive frame of mind," indicating higher well-being. (Table 3 in the article by Runge et al. [19] provides more detail.)

The number of CGM-related observational studies focusing on time in glucose ranges and PROs is limited. The FUTURE trial (35) included PRO measures along with CGM-derived parameters such as TIR, TBR, and TAR as secondary outcomes. In this observational, multicenter, prospective real-world cohort study, the authors investigated the impact of CGM use on quality of life and glycemic control in people with type 1 diabetes. General and diabetes-specific quality of life remained unchanged on a high level after 12 months of CGM use, while treatment satisfaction improved. The authors also found a significant decrease in time spent in hypoglycemia; however, this improvement was at the expense of less TIR and greater TAR. These findings are in line with results of the RESCUE trial (36), which also investigated CGM parameters and found improvements in quality of life and especially in fear of hypoglycemia in a real-world setting.

Similar to interventional studies, these real-world observational studies did not specifically analyze the associations between CGM parameters and aspects of well-being. Furthermore, they do not allow for an assessment of the relationship between PROs and CGM parameters on a day-to-day basis. To assess the associations between glycemic control and self-reported mood (as a PRO measure) more closely, Hermanns et al. (37) equipped 36 people with type 1 diabetes with a blinded CGM system for 48 hours and asked them to rate their mood multiple times during this period. Mixed regression analyses of glucose levels and mood ratings showed that, as glucose levels increased, participants were more likely to report feelings of anger and tension. However, the study did not find any association between mood and glucose variability.

In 2017, Wagner et al. (38) took a similar approach to investigate the associations between CGM-derived parameters, diabetes self-care behaviors, and affect in people with type 2 diabetes. On 7 consecutive days, the 50 participants wore a blinded CGM and reported negative or positive affect twice daily. Between-person analyses revealed that higher mean levels of self-reported negative affect and variability in negative affect were associated with higher mean glucose, more TAR, and less TIR.

Polonsky and Fortman (39) aimed to investigate how daily glycemic control is associated with mood. Over a 2-week period, participants using rtCGM completed a brief online mood and well-being survey every night. The study found significant associations between daily glycemic metrics and well-being; increases in daily TIR were significantly associated with better mood ratings in the evening. However, daily changes in TBR and glycemic variability were not significantly related to well-being (i.e., mood ratings).

To systematically address glycemic variability, Muijs et al. (40) reviewed empirical evidence on glucose variability and mood in adults with type 1 or type 2 diabetes. Of eight studies included in the systematic review, four used CGM to assess glycemic control. Although the overall results did not provide clear evidence of a link between glucose variability and mood on a daily basis, the authors reported evidence suggesting a significant relationship between a higher rate of postprandial glucose increase and more negative mood in people with type 2 diabetes. Furthermore, a possible beneficial effect of lower glucose variability on depressive mood emerged in adults with type 1 diabetes. However, both findings warrant further research.

The recent approaches by Wagner et al. (38) and Polonsky and Fortman (39) show the potential of combining CGM data with other repeated-sampling methods as a promising way to assess the association between aspects of glycemic control and well-being of people with diabetes on a more

"molecular" level. The observational data from the studies discussed above do not allow for any conclusions about causation (i.e., that current high or low glycemic levels lead to negative affect or vice versa). Muijs et al. (40) emphasized that high-quality studies are needed to investigate larger populations over a longer time period.

Current Studies Using Ecological Momentary Assessment and CGM

Three projects currently underway to address the associations between glucose and well-be of ing include larger samples and have longer observation periods. They all aim to provide an in-depth understanding of how glucose affects PRO measures such as well-being and diabetes distress and vice versa. These projects include the FEEL-T1D trial in the United States (41), the international HypoRESOLVE project (work package 6: psychological burden) (42), and the DIA-LINK studies in people with type 1 diabetes (NCT03811132) and type 2 diabetes (NCT04438018) in Germany.

Common to all is the aim to better understand the associations between glucose and parameters of well-being on a daily basis. This understanding can be achieved using ecological momentary assessment (EMA) to measure PROs in combination with CGM. EMA is a methodology that allows the repeated sampling of PROs in real time, in a real-world setting (43). Surveys are usually administered several times daily via smartphone. Previously, PROs have been assessed via questionnaires that offer a summary rating (e.g., covering the past 2–4 weeks). Much like A1C, questionnaires offer a retrospective assessment of mean well-being over a longer period of time. In people with diabetes, the benefits of the EMA approach over retrospective questionnaires therefore mirrors the advances of CGM over A1C. Thus, the combination of EMA and CGM could overcome the methodological limitations (e.g., recall bias, recency effect, and peak-end rule effect) of using retrospective questionnaires as measure of PROs and A1C as a retrospective measure of glycemic control.

Although published findings from these projects are pending, there is some preliminary evidence from interim analyses of 152 people with type 1 diabetes in the DIA-LINK study. Participants were surveyed four times per day for 18 days on different aspects of well-being. The preliminary results indicate that better mood and higher subjective energy ratings were predicted by higher TIR and lower TAR in the 90 minutes preceding these ratings, suggesting an imme-diate effect of glucose values on PROs (44). Furthermore, hypoglycemia-related worries were associated with more TBR and higher glucose variability (i.e., CV), whereas hyperglycemia-related worries were associated with lower TIR, higher TAR, and higher mean glucose (45). There is also preliminary evidence that higher glucose variability may be associated with feelings of guilt regarding diabetes self-management as well as with feeling overwhelmed by living with diabetes (46).

These preliminary findings suggest that different CGM-derived parameters of glycemic control have differential effects on PROs. Whereas TIR and TAR might play a role in general mood or well-being and hyperglycemia-related PROs, TBR and glucose variability seem to be more relevant for hypoglycemia-related PROs and the cognitive representation of the burden of diabetes management. Further analyses are needed to substantiate these findings.

Implications for Future Research and Clinical Practice

TIR and other metrics are increasingly deployed as outcome measures in research and clinical practice. With new glycemic targets and evidence supporting their clinical validity with regard to long-term complications, these CGM-derived parameters of glycemic control will also be increasingly important for people with diabetes and daily diabetes management. As evidenced by the survey from Runge et al. (19), TIR is already perceived by people with diabetes as an important factor influencing their daily life. However, evidence is still limited regarding the actual effect of TIR and other metrics on well-being (Table 1). Evidence from interventional studies suggests a disparity between the improvements in CGM-derived parameters and improvements in PRO measures, with large effects on glycemic outcomes but only small effects on PROs (28).

Incongruent improvements in CGM and PRO measures found in interventional studies might be the result of inadequate questionnaires that fail to mirror real-time effects of CGM on glycemic control. Current questionnaires may be too generic to capture the impact of time in glucose ranges on the well-being of people with diabetes. This problem results in differences in the temporal resolution of assessing glucose in real time via CGM and PROs via retrospective questionnaires that require a summary rating. Thus, recent approaches have implemented a more real-time assessment of PROs and are thus able to analyze more immediate effects between glucose and well-being. Looking at these immediate associations on a daily or hourly level, there is evidence indicating that greater TIR is indeed associated with better mood (39,44), and higher TAR/lower TIR is associated with negative affect (38).

The analysis of immediate associations using CGM and EMA raises questions about the mechanistic nature of the association between glucose and well-being. Specifically,

TABLE 1 Overview of the Evidence on Associations Between CGM-Derived Parameters of Glycemic Control and Patient-Reported Outcomes

	Type of Analysis	Type of Evidence	Limitations
Interventional studies	• Randomized controlled trials on the efficacy of CGM and AID systems • Congruent improvements of CGM-derived parameters of glycemic control and PROs, indicative of an association	• Large effect sizes regarding improvement of CGM-derived parameters • Small to medium effect sizes regarding improvement of PROs	• No direct analysis of associations • Rather optimal baseline levels of PRO measures, possible lack of room for improvement
Observational studies	• Direct analysis of the association between CGM-derived parameters and PROs	• Higher TIR associated with better mood • Higher mean glucose/more TAR associated with negative affect/anger	• Rather small sample sizes • No causality
Ongoing studies	• Using EMA and CGM to analyze immediate effects of CGM-derived parameters on PROs and vice versa	• Planned: real-time effects of glucose on PROs and vice versa • Planned: intraindividual patterns	• Publications in peer-reviewed journals pending

ongoing and future research could analyze whether mood and well-being are a function of glucose levels. This issue raises the further question of whether mood and well-being are influenced by seeing a single situational glucose value or more affected by the sum of aggregated glucose values (i.e., TIR) over a longer period of time. Further research is also needed to analyze whether it is primarily a direct physiological effect of glucose on mood or a more cognitive effect mediated by the knowledge that optimal or suboptimal glycemic control reflects personal diabetes management and health-related risks. This question could be assessed by comparing blinded CGM use with unblinded CGM use and the resulting associations with PROs. This issue is particularly relevant because, in contrast to the current glucose value and fluctuations, some CGM-derived parameters such as TIR, TBR, and TAR are not directly visible for the person with diabetes but must first be analyzed in CGM data software.

Using the combination of CGM and EMA could also inform individualized medicine in that associations between time in glucose ranges and well-being may not be influenced by fixed absolute ranges but rather by individual glycemic targets. The relative deviation from these glycemic targets might be more important for well-being than time spent in a predefined range. In addition, CGM and EMA allow for "$n = 1$" time-series studies and the analysis of intraindividual associations between glycemic parameters and well-being. This approach could tell clinicians and researchers more about the quality of glycemic control and whether it is influenced by psychosocial factors. Analyzing such intraindividual patterns may also resolve some inconsistencies found when analyzing physiological and psychosocial variables, such as the inconclusive evidence of a link between worse glycemic control and depression (47).

To summarize, there is preliminary evidence suggesting that higher TIR is associated with better mood or less anger and negative affect and that TBR is associated with fear of hypoglycemia. However, further research is needed focusing on a more precise timing between the assessments of glucose and PROs. To better understand the association between glucose and well-being, it is necessary to assess both at the same time when they actually occur. This goal can be achieved by combining CGM for measuring glucose with EMA for measuring well-being and other PROs. EMA also constitutes a promising tool for interventional studies, as well as for clinical practice, to gain in-depth insights in patients' individual associations of glucose levels and well-being.

DUALITY OF INTEREST

D.E. has received speakers' honoraria from Abbott Diabetes Care, Berlin Chemie, Dexcom, Roche Diabetes Care, and Sanofi. B.K. is an advisory board member for Ascensia Diabetes Care, Berlin Chemie, Medtronic, Novo Nordisk, and Roche Diabetes Care, has received speakers' honoraria from Abbott, Ascensia Diabetes Care, Berlin Chemie, Lilly, Novo Nordisk, and Roche Diabetes Care, and has received grants in support of investigator trials from Abbott, Berlin Chemie, and Roche Diabetes Care. N.H. is an advisory board member for Abbott, Lilly, Novo Nordisk, Roche Diabetes Care, and Ypsomed, has received speakers' honoraria from Abbott, Berlin Chemie, Lilly, Novo Nordisk, and Ypsomed, and has received grants in support of investigator trials from Abbott, Berlin Chemie, Dexcom, Roche Diabetes Care, and Ypsomed. No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

D.E., L.P., and N.H. wrote the manuscript. D.E. and L.P. reviewed the literature. A.S. and B.K. revised the manuscript and contributed to the discussion. All authors approved the final version of the manuscript. D.E. and L.P. are the guarantors of this work and, as such, had full access to all the data in this review and take responsibility for the integrity of the data and the accuracy of the review.

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