# Connecting the Dots: Validation of Time in Range Metrics With Microvascular Outcomes

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The landmark Diabetes Control and Complications Trial (DCCT) identified the relationship between intensive diabetes management for those with type 1 diabetes (T1D) and a delay in the onset or progression of microvascular complications, shifting the paradigm of clinical care for this chronic medical condition (1). Importantly, the data from that trial continue to have a lasting legacy as they can now be analyzed to inform present-day questions. An example of this comes from the article by Beck et al. in this issue of *Diabetes Care* (2) that concisely states the primary implication of the article in its title, "Validation of Time in Range as an Outcome Measure for Diabetes Clinical Trials." In recent years, and with increasing use of continuous glucose monitoring (CGM), the ability to classify sensor glucose levels into various ranges has been feasible. Yet, some have questioned the validity of using these measures as a surrogate outcome measure in ongoing and future clinical trials. Indeed, some have called for a "modern-day" DCCT assessing whether CGM and a greater time in range (TIR) would result in fewer microvascular end points compared with self-monitoring of blood glucose (with intermittent masked CGM). Unfortunately, the duration of time, funds required, and ethical concerns given clinical equipoise regarding the benefits of the technology would make completion of a rigorous randomized controlled trial a near-impossible feat.

Recognizing the wealth of data that the DCCT affords, Beck et al. (2) found a creative solution to assess the hypothesis of whether TIR could serve as an outcome measure for future trials. Specifically, they capitalized on the glucose values captured seven times daily every 3 months during the course of the 6+ years of the DCCT. This allowed them to calculate the percent TIR of glucose values between 70 and 180 mg/dL and show a robust association with development of both diabetic retinopathy and microalbuminuria. As the authors highlight, a difference in TIR of 10–12% (2.5–3 h/day) was seen between the groups of those who developed complications versus those who did not. With each 10% drop in TIR, there was an increase in risk of retinopathy by 64% and of microalbuminuria by 40%.

Using more modern-day retrospective CGM between 2005 and 2012, Lu et al. (3) recently reported on 3,262 individuals with type 2 diabetes (T2D). Overall results were similar to those found by Beck et al. (2); TIR in T2D was negatively associated with diabetic retinopathy. Those with vision-threatening retinopathy had the lowest TIR.

The idea of using percent TIR as an important outcome in trials and clinical practice is not new (4,5), and many have called for us to look "beyond A1C" (6,7). Yet, prior to the articles by Beck et al. (2) and Lu et al. (3), no outcomes-based evidence to support the use of TIR existed. A primary conclusion drawn in the study by Beck et al., and one we agree with, is that "TIR is strongly associated with risk of microvascular complications" and therefore it should be accepted as an end point for clinical investigations (2,3). Furthermore, TIR has added value beyond the accepted gold standard of A1C. Discussing how the authors arrived at this conclusion and how it fits in the current framework of diabetes management requires us to first provide some historical context.

A1C was discovered in 1968 and it began to be used for clinical care in the early 1980s (8). As performance of the test improved, clinical uptake was relatively quick, and by the end of the 1980s use of this objective measurement of glycemic control was standard of care; in fact, routine measurement of A1C was part of the first American Diabetes Association "Standards of Care" published in 1989 (9). Conduct of the DCCT was

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feasible, in part, because of the ability to conduct home blood glucose monitoring, measure A1C levels, and utilize insulin pump therapy as a means to intensify the insulin regimen. In recognition of the limitations of A1C measurements, individuals with hemoglobinopathies, as well as those with renal and liver disease, were excluded from study participation. Despite the fact that investigators at the time cautioned it was not an "A1C study" but rather a study on the effectiveness of two therapies (standard vs. experimental intensive insulin therapy), the DCCT and many other studies have been interpreted as exactly that: the goal of diabetes therapy is to improve the A1C to a certain number, depending on the clinical situation. To this day, A1C targets are based on the interpretation of the DCCT in T1D and the UK Prospective Diabetes Study (UKPDS) in T2D (10).

Even in the 1980s, it was recognized that many clinical situations could result in falsely low (and occasionally falsely high) A1C levels (11). Since 1990, it has been known that for any given A1C value there can be an extremely wide range of mean blood glucose levels (12). What was not well appreciated until the introduction of CGM was how varied A1C could be between two people without any known interfering conditions (13). In fact, someone with an A1C of 7% could possibly have a higher mean glucose level than someone with an A1C of 9% (13). Current practice consists of measurement of A1C levels to help categorize degree of glycemic control and therefore infer potential risk of microvascular complications. Yet, without the aid of CGM data and determination of the mean sensor glucose level that equates to this standard laboratory measurement, clinicians remain somewhat blind to the degree of dysglycemia their patients are experiencing. Furthermore, retrospective review of CGM data affords the ability to assess TIR, allowing for optimization of insulin doses and diabetes management plans.

Over the past decade, CGM has improved in accuracy, affordability, and penetration into clinical practice. Indeed, recent data from the T1D Exchange highlight that from the time of the registry's inception in 2010–2012 to 2016–2017, use of CGM had risen fourfold, from 7% to 28% (14). Thus, although this is a drastic rise in CGM use, only one-quarter of T1D Exchange registry participants were using this technology as of the last data collection period. With the ability to use sensor glucose readings without confirming with fingerstick glucose readings and the need for sensor therapy to drive automation of insulin delivery, use of this technology is quickly becoming the standard of care, especially for those with T1D. CGM glucometrics have evolved beyond assessing means and variability statistics, and both patients and providers agree that use of TIR as a primary metric for diabetes control is essential as it is easily understood by all involved in care and provides guidance on where efforts should be focused (i.e., reduction of hyperglycemia or avoidance of hypoglycemia). For clinical care, knowing the TIR (including time above and below range) gives a global assessment of control, but to better understand where there may be greater hyperglycemia, hypoglycemia, or variability, assessment of an ambulatory glucose profile is needed. Furthermore, given the limitations of A1C, the question is whether it is possible to use CGM data as an alternate metric for individuals, as this can then be used as an end point for clinical trials, including those used for regulatory purposes. Up until now, the greatest challenge with CGM data was that there were no studies correlating TIR and microvascular complications.

For the DCCT with the quarterly seven-point capillary glucose profiles from all 1,440 patients over the course of the 6+ years of the study, the question of the association between TIR and development of microvascular complications could be explored. The conclusions are what many have been awaiting since we started using CGM, yet the actual TIR may be surprising to some given how well we can manage diabetes today; the intensive therapy group only had a TIR of 52%, while the standard group had a TIR of 31%. TIR was substantially lower in those who developed microvascular complications compared with those who did not. In fact, for the outcome of retinopathy, TIR was ~12% lower, while for those with microalbuminuria there was a ~10% lower TIR. The difference in TIR between people developing and not developing eye or kidney disease equates to about 2.5 h each day.

While these findings are provocative, it is important to note that use of CGM could have produced even more striking results. As sensor glucose values are measured every 5–15 min, depending on the sensor, there is a 40-fold increase in the data collected with CGM as compared with the seven-point measurements available for this analysis. However, prior publications have demonstrated similar TIR assessment when comparing data from CGM and blood glucose meters (15,16). One theoretical concern is that as participants in the DCCT conducted seven-point measurements only every 3 months, it is possible that on the days when increased monitoring was required, participants were more diligent with their diabetes management.

After the DCCT was completed, the observational Epidemiology of Diabetes Interventions and Complications (EDIC) study continued reporting outcomes. It is noteworthy that despite A1C levels being the same in the two treatment groups for 18 years of follow-up in EDIC, "metabolic memory" during this time interval resulted in the experimental group developing less retinopathy (17). Additionally, after a mean of 27 years in both the DCCT and EDIC studies, less cardiovascular disease and all-cause mortality were noted (18). The obvious question is whether TIR from the seven-point glucose profiles can be extrapolated to the EDIC findings. Since the TIR from the intervention in the DCCT predicted DCCT outcomes, and there was no other intervention in EDIC, we believe the study by Beck et al. (2) can be extrapolated to this concept of metabolic memory, even though the molecular mechanisms are not completely understood. Furthermore, although it had a different design, the study by Lu et al. (3) in individuals with T2D is consistent with the hypothesis that glucose, and more specifically TIR, is also predictive of diabetic retinopathy in T2D.

Once the DCCT proved the intimate relationship between the intensification of insulin regimen leading to more targeted glycemic control and delayed onset and progression of microvascular complications, efforts were focused on incorporating this tool into clinical practice. Although investigators were already using this measurement as a primary outcome for clinical trials, its clinical application took time. What was necessary at the time was to educate and train

diabetes care and primary care practitioners on the benefits of knowing the A1C of a person with diabetes seen in their clinic. Direct-to-consumer public service announcements to "know your A1C" also became widespread.

We believe that along with A1C, the present analysis provides the evidence that TIR should be accepted as a primary outcome for future clinical investigations. We encourage the conduct of a confirmatory prospective observational study assessing TIR and microvascular complications. Indeed, longitudinal registry data could be used to answer these questions. The real question for researchers and clinicians is how much more data are required on use of the TIR end point for patient care, study outcomes, and regulatory decisions. Certainly, it would be interesting to see how the DCCT TIR data predict the results from the follow-up EDIC study. However, it is also critical to understand the current landscape of diabetes management that includes not just technological advancements but also alterations in screening and treatment for comorbid conditions, including stricter blood pressure and lipid targets and routine use of ACE inhibitors and statins, for example. Indeed, the impact of TIR in the current era may have different implications than what was observed with the DCCT findings; however, we would maintain the same could be said for A1C.

Given the known problems with A1C, which is a biomarker of glucose, we believe it is appropriate to use TIR as a valid end point given the clear toxicity of chronic hyperglycemia (19). It is also important to note that TIR can inform providers and patients where efforts should be focused to help individualize a patient's diabetes care plan, in hopes of minimizing microvascular complications. In an era of personalized medicine, tracking an individual's progress in regard to TIR achieved allows for realistic goals to be developed in conjunction with providers. Unlike for A1C measurements, it will be easier for all diabetes care providers, including those in primary care, to convey this information and educate patients. With the advent of ambulatory glucose profile reports, people with diabetes can quickly garner from interpretation of their current data where changes need to be made and why certain dose adjustments may assist in achieving glycemic goals (20). No longer are we left to connect the dots of intermittent blood glucose monitoring to build a story about risk of microvascular complications; we can see the issues from every angle.

While to some it may seem like A1C is "outdated," we would maintain that this biomarker should continue to be used as a tool for both clinical care and research. A1C has a proven track record but provides different information than TIR, thus a combined outcome for these two metrics seems justified. In addition, particularly for clinical care, it is not realistic to assume CGM will become so popular that there would not be a need for A1C.

What the article by Beck et al. (2) provides is a call to action. Our job will be to inform all our colleagues of the benefits of assessing TIR, educate those who are unfamiliar with it, and provide the tools necessary to people with diabetes. Regulators will need to rethink the end points chosen in conjunction with investigators for clinical trials. Insurers may find these data assist them in allowing for coverage of such devices; after all, if we can minimize long-term microvascular complications, that should be of benefit. Advocacy groups who have worked tirelessly to assure no person with type 1 diabetes is denied use of CGM will have their argument strengthened by these data. Finally, device manufacturers will need to continue to innovate CGM technology, making the duration of wear longer, ensuring the footprint of the device is smaller, and finding clear and compelling ways to make the data collected easily interpretable.

At the conclusion of the DCCT, members of the Joslin Clinic wore buttons stating "I told you so. —E.P. Joslin" (21). For many it comes as no surprise that lower TIR has now been associated with microvascular complications. In the midst of this technological revolution, embracing CGM metrics for both trials and treatment makes sense. Maybe it is time to remake the buttons.

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