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Will Continuous Glucose Monitoring Metrics Replace Hemoglobin A1c in Assessing the Risk of Retinopathy (and Other Complications) in Patients with Type 2 Diabetes?

Time in range (TIR) is an important contemporary diabetes measurement derived from continuous glucose monitoring (CGM) data [1]. International consensus recognizes TIR as a measure of glycemic control that provides more useful information than hemoglobin A1c (HbA1c) alone [2].

In this issue of "Clinical Diabetology", Pratama et al. presented a systematic review and meta-analysis exploring the link between time in range and diabetic retinopathy (DR). The authors showed that lower TIR is significantly associated with DR [3]. Similar correlations are well known for hemoglobin A1c — higher HbA1c indicates poor metabolic control of diabetes and higher risk of DR [4–6]. The question arises which of these two measures better assesses the risk of retinopathy (but also other diabetes complications) in patients with type 2 diabetes.

Rapidly evolving CGM technology allows for a very deep insight into glycemia. The traditional gold standard for evaluating glycemic control is hemoglobin A1c. Continuous glucose monitoring, however, offers insights that HbA1c cannot provide. HbA1c evaluates static glucose exposure and does not account for intraday glycemic fluctuations that can lead to acute events such as hypoglycemia or postprandial hyperglycemia, both of which are associated with diabetic complications [7–10]. CGM tracks glucose levels consistently, detects fluctuations in blood glucose (glycemic variability), monitors how quickly glucose levels change, assess time spent in hyper- or hypoglycemia and provides a better understanding of an individual's unique glycemic profiles. Continuous glucose monitoring additionally overcomes the problems inherent in HbA1c, such as interference with this metric by anemia, hemoglobinopathies, pregnancy, chronic kidney disease, liver disease.

So far HbA1c has been the sole method systematically studied to assess the risk of diabetes-related complications [11], however, more and more data are available indicating TIR as a metric for correlation with micro- and macrovascular complications [12–19]. Nevertheless, it should be noted that there are no established ranges for TIR that specifically reduce diabetes complications [20]. Most adults with type 1 or type 2 diabetes are recommended to spend at least 70% of the day (around 17 hours) in the target glycemic range of 70 to 180 mg/dL, which corresponds to the approved

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hemoglobin A1c target of approximately 7% [2] and may constitute a threshold value for increased complications' risk. This is, however, not yet confirmed in any prospective outcome study.

There are only very limited data comparing TIR and HbA1c in predicting complications in diabetes. In a cross-sectional analysis of 161 patients with type 1 diabetes, both TIR and HbA1c were associated with adverse consequences of the disease. The authors concluded that TIR may be a better predictor than HbA1c for any complication and microvascular complications, while HbA1c may be a better predictor of macrovascular complications [21]. TIR has been shown to have an inversely linear relationship with HbA1c [22, 23]. However, recently published study by Eliasson et al. [24], besides a strong association between glycated hemoglobin and TIR, describes the relationship between HbA1c and other CGM metrics, such as time above range (TAR) and CGM mean glucose.

A question arises: which CGM parameter would be the best predictor of diabetic complications? As of now, there is no evidence-based answer to this question. One might consider that if prolonged hyperglycemia in patients with poor metabolic control is the primary cause of chronic complications in diabetes, higher TAR appears to be a more natural predictor of them than TIR. Additionally, high TIR can result not only from low TAR but also from extended time below range (TBR). Therefore, any predictions based on TIR should be adjusted considering TBR. This latter parameter needs also to be considered in predicting retinopathy. There is a substantial body of evidence, although mainly from preclinical studies, linking this complication of diabetes to hypoglycemia [25–27].

Further research is needed to address the above-mentioned question and to respond to another one: Is HbA1c measurement necessary in patients using CGM? It appears that it is not, as CGM metrics may perform equally well in assessing blood glucose control and the risk of complications. Additionally, HbA1c can be calculated from blood glucose values. It seems therefore quite possible that in the future, at least in patients using CGM and glucose meters, we will use only a calculated HbA1c value, as at present we use only a GFR value calculated from creatinine concentration.

Understanding of how TIR, TAR and TBR relate to HbA1c is important and discussion on this issue is still ongoing. There is a need to perform large-scale studies to establish clear associations between CGM parameters and HBA1c as well as to compare their usefulness as predictors of the risk of complications in patients with diabetes. For now, available data suggest that monitoring CGM metrics could be a reliable way to assess glucose exposure, potentially reducing the need for HbA1c testing in clinical practice.

Conflict of interest

The authors declare no conflict of interest.

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