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Time in Range: Unveiling the Correlation with Diabetic Retinopathy in Type 2 Diabetes: A Systematic Review and Meta-Analysis

ABSTRACT

Objective: Research has established an association between glycemic control and retinopathy progression; however, the use of continuous glucose monitoring (CGM) and diabetic retinopathy (DR) progression remains less explored. Our study aims to explore the link between time in range (TIR) and DR and its clinical implications.

Materials and methods: Following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guideline, we conducted a systematic review by searching databases such as PubMed, EBSCO, and ProQuest, supplemented by manual exploration. Studies reporting TIR or other CGM-derived metrics in association with DR were included. The quality of each study was evaluated using the Newcastle-Ottawa Scale (NOS). Review Manager 5.4 software, was used to performed a meta-analysis with random-effects model.

Results: The meta-analysis of five studies indicated significant associations between CGM-derived metrics and diabetic retinopathy. TIR exhibited a mean difference of –6.44 (95% CI: –8.10, –4.78, $p < 0.001$), standard deviation (SD) showed a mean difference of 0.20 (95% CI: 0.16, 0.24, $p < 0.001$), mean amplitude of glycemic excursion (MAGE) displayed a mean difference of 0.45 (95% CI: 0.31, 0.58, $p < 0.001$), and coefficient of variation (CV) demonstrated a mean difference of –0.99 (95% CI: 0.43, 1.55, $p = 0.0006$). Stratification by TIR percentage (< 70% vs. ≥ 70%) revealed an odds ratio of 2.06 (95% CI: 0.85, 4.97, $p = 0.11$) for diabetic retinopathy risk, although statistically insignificant.

Conclusions: Lower TIR is significantly associated with DR in T2D patients. Furthermore, higher SD, MAGE, and CV were linked to the presence of DR. (Clin Diabetol 2024; 13, 3: 132–139)

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Keywords: diabetic retinopathy, type 2 diabetes, continuous glucose monitoring

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Introduction

Effective management of type 2 diabetes (T2D) revolves around glycemic control, with hemoglobin A1c (HbA1c) being a central parameter [1]. HbA1c offers a retrospective overview of blood glucose levels spanning several months, providing valuable insights into long-term glycemic regulation [2]. However, its usage is limited by factors such as age, hemolytic anemia,

or conditions that affect the interaction between red blood cells and glucose-bound hemoglobin [2]. Additionally, HbA1c has more limitations such as capturing the fluctuations and patterns of glycemic variability, which lead to differences between mean glucose levels and HbA1c readings [2, 3]. Among the microvascular complications associated with T2D, diabetic retinopathy (DR) is a concern, affecting approximately one-third of T2D patients [4, 5]. It is considered a leading etiology contributing to global blindness [6]. Research showed the prevalence of DR reaching 22.27%, highlighting the crucial need for timely recognition and intervention to reduce any complications [7].

Continuous glucose monitoring (CGM) emerges as a promising new technology in management in T2D [8]. CGM offers a real-time variability of glycemic patterns, offering valuable insight into an individual's glucose levels. In 14 days, CGM provides time in range (TIR), the percentage of time glucose concentrations remain within the range of 70 to 180 mg/dL [8]. Unlike HbA1c, CGM could capture the fluctuations and patterns in glucose levels, providing a more comprehensive picture of an individual's glycemic profile [8, 9]. Furthermore, nocturnal, or asymptomatic hypoglycemia, can be mitigated or minimized. This results is an enhancement of the quality of life for patients with T2D [10]. Additionally, metrics such as mean amplitude of glycemic excursion (MAGE), coefficient of variation (CV), and standard deviation (SD) provide a further understanding of glucose variability and consistency [11]. Research indicates that CGM correlates with HbA1c, thus establishing both approaches as reliable means for monitoring glycemic control. However, CGM has the advantage of detecting hypoglycemia, a capability lacking in HbA1c measurements [12].

Research has established an association between glycemic control and retinopathy progression. A study revealed a 64% increase in the hazard ratio for retinopathy progression with every 10% decrease in TIR [13]. Based on these results, we carried out a systematic review and meta-analysis to highlight the association between TIR and other CGM-derived metrics and DR. Furthermore, we will explore the practical implications for clinical strategies.

Materials and methods

This systematic review was carried out according to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) [14] and registered in PROSPERO (CDR42023452999).

Subjects

In devising search strategies to identify pertinent studies regarding the association between TIR and DR, we employed medical subject headings (MeSH) and unstructured text expressions. Our thorough search encompassed multiple databases, including PubMed, EBSCO, and ProQuest. For comprehensiveness, we manually reviewed the references of included studies and relevant reviews. Additionally, we searched Google Scholar to uncover any potentially overlooked literature. This exploration involved synonyms and variations of the terms 'time in range', 'continuous glucose monitoring', and 'diabetic retinopathy', restricted to the period from 2013 to 2023 (Suppl. File 1). We excluded studies that reported TIR but did not use CGM in their measurement or studies that reported TIR in type 1 diabetes. Moreover, we confined our investigation to articles published exclusively in English and Indonesian languages.

Research studies could be considered for inclusion if they met the following criteria.

- Designs: randomized controlled trial (RCT), prospective and retrospective studies, case-control, or nested-case control studies, and cross-sectional studies. Case series and case reports are excluded from the analysis.
- Population: T2D patients using CGM
- Intervention/Exposure: DR
- Control/Comparison: Non-DR
- Outcome: TIR and other CGM-derived metrics

Study design

Our study adopted a systematic review and meta-analysis approach to investigate the relationship between TIR in T2D patients and the presence of DR.

Data collection

We employed the Zotero reference manager to manage the identified studies. Initially, a deduplication procedure was done, followed by the evaluation of study titles and abstracts to determine eligibility. This evaluation was conducted independently by two co-authors (KGP and MA). If studies were deemed potentially relevant during this preliminary assessment, a comprehensive full-text review was undertaken. In instances of disagreement during the selection or quality assessment phases, these matters were deliberated with two other co-authors (YSA and NS) to reach a consensus. Relevant data was extracted to perform a qualitative synthesis. The extracted data encompassed details such as author, year of publication, geographical

locations, study designs, inclusion, and exclusion criteria, CGM model, CGM-derived metric (TIR in particular), diagnosis and classification of DR, the incidence of diabetic retinopathy and related key findings.

Outcome

The main outcome of the study was association between DR and CGM-derived metric, including TIR.

Risk of bias

The quality of each study was evaluated using the Newcastle-Ottawa Scale (NOS) [15]. It consists of three main components: Selection, Comparability, and Outcome. Each component is assessed based on predetermined criteria, with higher scores indicating better quality. Selection evaluates representativeness and appropriate selection criteria, Comparability assesses control of confounding factors, and Outcome examines outcome definition and ascertainment methods. Scores between 0–3 suggest significant limitations, 4–6 indicate moderate quality with some limitations, while scores of 7–9 represent good quality and minimal bias.

Statistical analysis

Our approach will involve a comprehensive qualitative synthesis, entailing the integration of data from both the textual content and tables of the studies encompassed. This synthesis is aimed at providing a concise recapitulation and explication of the attributes and discoveries of these studies, alongside delving into the interrelations among them. In cases where the studies demonstrate satisfactory uniformity in terms of design and comparator, we will undertake meta-analyses utilizing the random effects model. The assessment of the overall impact will involve the analysis of the mean difference, along with a 95% confidence interval (CI). For the evaluation of statistical heterogeneity, the I^2 statistic will be employed. The data will be consolidated and computed employing the statistical tool Review Manager (version 5.4, Cochrane Collaboration, Copenhagen Denmark).

Results

Study characteristics

A total of 582 studies were identified through a combination of three databases and manual searching, as depicted in Figure 1. Following a screening process, we ultimately incorporated five studies that investigated the relationship between TIR and various other CGM-derived metrics with DR [16–20]. These studies consisted of a combination of three cross-sectional and two prospective-cohort designs. Geographically, the distribution involved two studies conducted in Japan and three studies conducted in China. The cumulative participant count across all the studies included 7328 individuals, showcasing a diverse demographic range within the context of T2D. In terms of CGM utilization, Medtronic Inc. was highlighted in three studies, while the FreeStyle Libre Pro (Abbott Japan) and iPro 2 (Medtronic Inc.) CGMs were each employed in one study. A spectrum of CGM metrics was gathered throughout these investigations, with consistent measurements of TIR, SD, CV, and MAGE across multiple studies. The assessment of DR was conducted by experienced ophthalmologists in four studies, while non-mydriatic fundus photography was utilized in two studies to ascertain the presence and severity of DR. Furthermore, certain studies categorized DR into subtypes. All the included studies consistently show the connection between CGM metrics and diabetic retinopathy even when adjusting for risk factors and varying patient populations. For a comprehensive overview of study characteristics, refer to Table 1.Top of Form

Meta-analysis of CGM-derived metrics and diabetic retinopathy

The meta-analysis encompassed four CGM-derived metrics: TIR, CV, MAGE and SD. Three studies were employed to compare the TIR percentage between DR and Non-DR. The analysis revealed a mean difference of –6.44 (95% CI: –8.10, –4.78, $p < 0.001$) with moderate heterogeneity ($I^2 = 37\%$). This suggests a significant association between lower TIR and DR (Fig. 2). The analysis of SD, involving four studies, demonstrated a mean difference of 0.20 (95% CI: 0.16, 0.24, $p < 0.001$) with no heterogeneity ($I^2 = 0\%$), indicating a relationship between higher SD and DR (Suppl. File 2). Similarly, the MAGE analysis from three studies indicated a mean difference of 0.45 (95% CI: 0.31, 0.58, $p < 0.001$) with no heterogeneity ($I^2 = 0\%$), emphasizing that higher MAGE is associated with DR (Suppl. File 3). Additionally, the CV percentage analysis from three studies revealed a mean difference of 0.99 (95% CI: 0.43, 1.55, $p = 0.0006$) with substantial heterogeneity ($I^2 = 58\%$), highlighting the link between CV percentage and DR (Suppl. File 4). Furthermore, stratification based on TIR percentage was performed in two studies, with participants categorized as TIR < 70% and TIR ≥ 70% in accordance with American Diabetes Association (ADA) recommendations [21]. While not statistically significant, TIR< 70% exhibited an odds ratio of 2.06 (95% CI: 0.85, 4.97, $p = 0.11$) for the risk of DR (Suppl. File 5). These findings, with corresponding figures, collectively emphasize the significant associations between CGM-derived metrics and the presence of diabetic retinopathy.

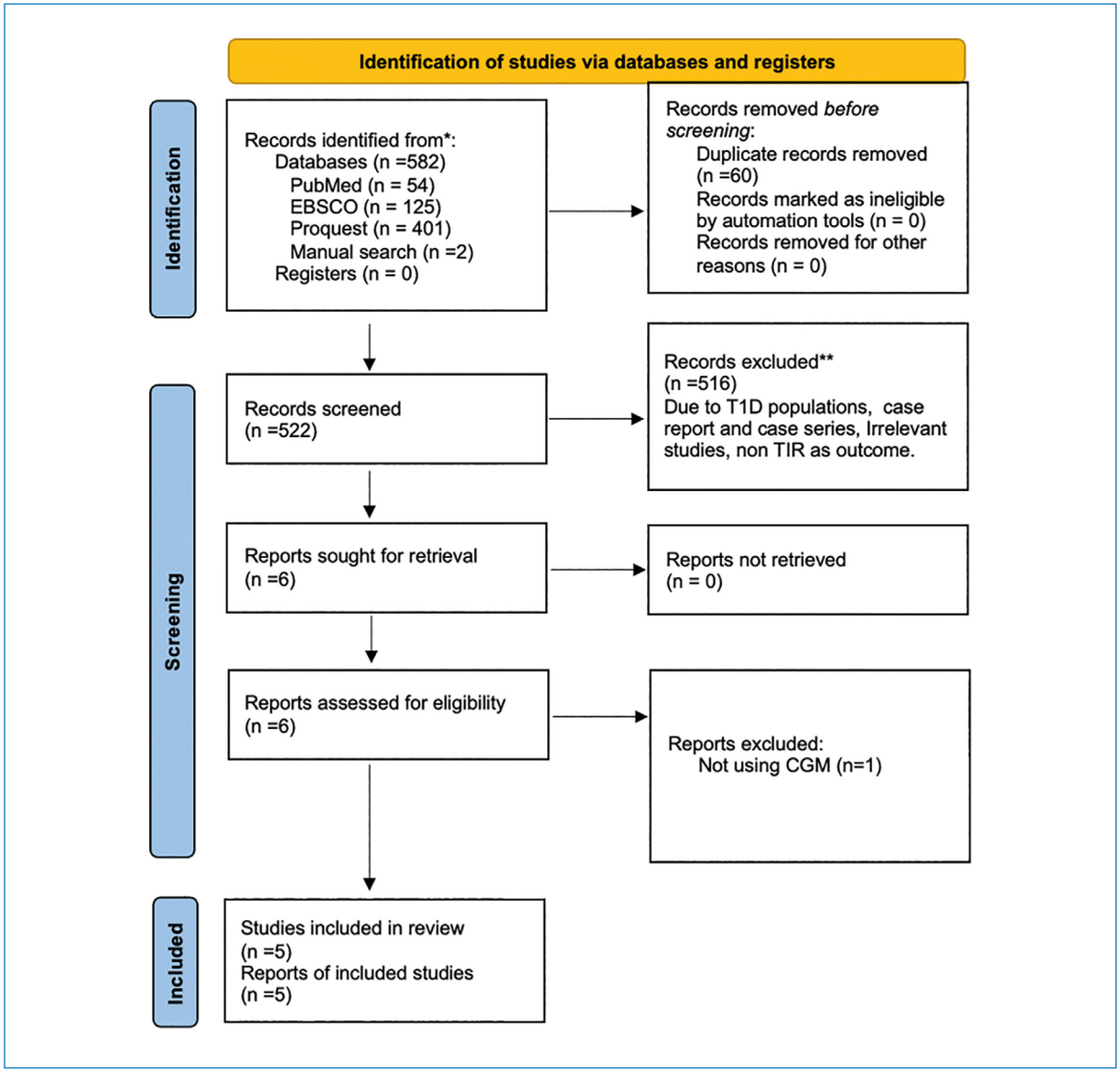

Figure 1. PRISMA Flow Diagram 2020
CGM — continuous glucose monitoring; T1D — type 1 diabetes; TIR — time in range

Risk of bias

Risks of bias were assessed using Newcastle-Ottawa Scale (Suppl. File 6). All of the study are considered good quality.

Discussion

HbA1c offers a basic view of average glucose levels over a few months but lacks insight into daily fluctuations and hypoglycemia [22, 23]. HbA1c mainly reflects high blood sugar and doesn't consider glycemic variability or daily pattern [12]. It can also vary due to conditions like anemia or kidney diseases, even when these conditions are not present, it can give a wide range of mean glucose value [13, 22].

In contrast, CGM metrics, like TIR, offer real-time insights into glycemic control [23]. CGM tracks time spent in target glucose ranges, identifying trends toward high or low blood sugar. [8] This technology catches quick changes in daily glucose levels, enabling prompt therapy adjustments [8]. It is important to note that CGM values can differ from lab-based measurements like HbA1c and mean plasma glucose [24].

Critical CGM metrics include TIR, time below range (TBR), and time above range (TAR), with the goal being to increase TIR while decreasing TBR [8]. This study also considered metrics like MAGE, CV and SD to assess daily glucose variability. Studies have demonstrated the usefulness of these metrics in assessing glucose

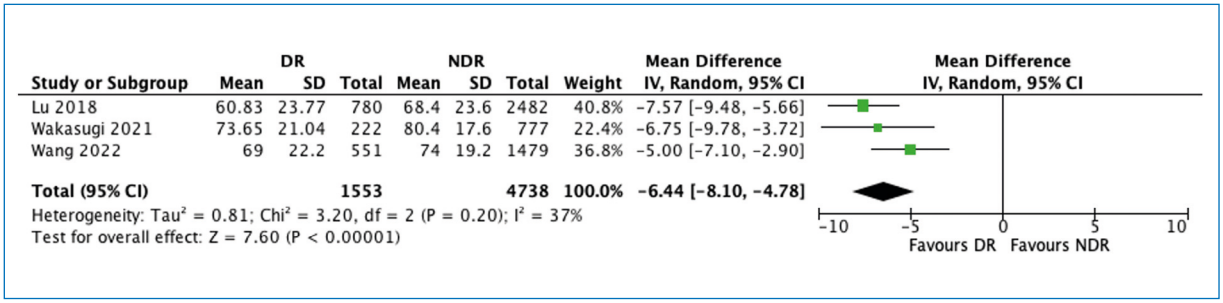

Figure 2. TIR and Diabetic Retinopathy
CI — confidence interval; DR — diabetic retinopathy; NDR — non-diabetic retinopathy; SD — standard deviation; TIR — time in range

variability and its link to microvascular complications in T2D [25, 26].

It has been widely recognized that persistently high levels of blood sugar play a significant role in causing severe complications and mortality in diabetes [27]. Numerous metabolic processes have been implicated in the vascular damage resulting from elevated blood sugar, including the polyol pathway, the accumulation of advanced glycation end products, activation of the protein kinase C pathway, and engagement of the hexosamine pathway [17]. However, presently, the fluctuation of daily blood glucose levels has emerged as a notable contributor to the development of micro- and macrovascular complications in diabetes [27]. Rapid fluctuations in blood sugar levels can lead to increased oxidative stress, inflammation, compromised endothelial function, and changes in gene expression [26].

A Cochrane review reveals that elevated HbA1c levels independently raise the risk of proliferative diabetic retinopathy (PDR) in T2D. Similarly, advanced retinopathy stages are linked to increased PDR risk [28]. Notably, two cohort studies emphasize the role of glycemic control assessed by HbA1c in diabetic retinopathy development and progression [29, 30]. A study by Tsujimoto et al. [31] revealed that after 4 years, individuals with good glycemic control experienced significantly lower incidence of vision-threatening retinopathy than those with poor control. However, there are participants with good glycemic control that also develop DR. Exploring the risk of DR in individuals with similar HbA1c levels but differing glycemic variation profiles, as assessed by CGM presents intriguing ideas for future research.

This study demonstrated that lower TIR and higher MAGE, CV SD significantly associated with DR. The association between TIR and DR in our study consistent with clinical trials reporting that glycemic control prevents or delays the development and progression of DR and development of microalbuminuria [13]. Moreover, current evidence demonstrated the associations between TIR and diabetes-related complications, such as DR, albuminuria, cardiovascular autonomic neuropathy, and peripheral neuropathy [23, 32, 33].

Several limitations should be considered in interpreting our findings. The relatively small number of available studies might impact the strength of our meta-analysis results. The prevalence of cross-sectional studies makes it challenging to establish cause-and--effect relationships and understand the underlying mechanisms. Additionally, the regional focus of the studies in Asia limits the generalization of our conclusions to broader populations.

The use of different CGM models across studies introduces potential heterogeneity in data interpretation. CGM devices from different manufacturers may vary in accuracy, calibration requirements, and data interpretation algorithms, influencing the consistency of CGM-derived metrics across studies. Variability in sensor placement, calibration techniques, and patient adherence further adds to the diversity in CGM data. Moreover, variations in CGM data reporting could affect the consistency of our findings.

Despite these limitations, our study has practical implications and suggests directions for future research. Our results can aid in identifying individuals at a higher risk of DR, enabling timely interventions. Notably, the variability in glycemic profiles among patients with similar HbA1c levels emphasizes the need for tailored approaches in managing DR and related complications.

To enhance our understanding, future studies could explore longer follow-up durations and employ prospective designs to uncover causal relationships between specific glycemic patterns and DR onset or progression. Intervention studies focusing on improving TIR through targeted therapeutic interventions, such as medication adjustments, lifestyle modifications, or

Table 1. Characteristics of Studies

Author (year)	Country	Design	N	CGM Duration	Study Population	CGM Brand	CGM Metrics Reported	DR diagnosis	Classification of DR	Key Findings
Hayashi [16] (2023)	Japan	Cross-sectional	107	48 hours	T2D undergoing maintenance HD	System Gold (Medtronic Minimed, Northridge, CA) in 40 people, and Medtronic iPro2® CGM (Medtronic Minimed) in 67 people	TIR, mean glucose, CV, SD, GMI	Preproliferative or proliferative retinopathy diagnosed by experienced ophthalmologists within 6 months of CGM attachment	Not specified	Higher TIR resulted in lower rate of DR
Wang [17] (2022)	China	Cross-sectional	2.030	7 days	18–80 years old T2DM patients with complete CGM dat	iPro 2; Medtronic Inc, Northridge, CA, USA)	TIR, AUC_{IR}, SD, CV, GMI	Screening involved the use of non-mydriatic fundus photography. In cases where the outcomes were unclear, an experienced ophthalmologist would examine further	Not Specified	For every 10% decrease in TIR, the risk of DR increases by 8% (95% CI 1.03–1.14). With every 10% reduction in AUC_{IR}, there was a corresponding 7% increase in risk (95% CI 1.02–1.13).
Wakasugi [18] (2021)	Japan	Prospective-Cohort study	999	14 days	30–80 years old T2DM patients, receiving treatment with no treatment changes for 6 months	The FreeStyle Libre Pro (Abbott Japan, Tokyo, Japan) CGM (FLP-CGM) device	TIR, Mean glucose, SD, CV, MAGE, LBGI, HBGI, MODD	The presence and severity of DR were determined by trained ophthalmologists.	SDR, PPDR, PDR	CGM-derived metrics concerning both daily and inter-day fluctuations in glucose levels are notably linked to the severity of DR This association remains significant even after accounting for diverse risk factors.
Lu [19] (2018)	China	Cross-sectional	3.262	72 hours	≥ 18 years old, T2DM, stable glucose-lowering regimen over previous 3 months	Medtronic Inc, Northridge CA	TIR, SD, CV, MAGE	Fundus photography using digital nonmydriatic camera	Mild NPDR, Moderate NPDR, VTDR	TIR assesed by CGM is significantly associated with DR.
Lu [20] (2019)	China	Prospective-Cohort study	2927	72 hours	All patients were taking a stable antidiabetic regimen for the previous 3 months. Diabetes was diagnosed according to the 1999 WHO	Medtronic Inc. (Northridge, CA, USA)	SD, CV, MAGE	DR was diagnosed by an ophthalmologist blinded according to International Classification of DR using fundus photography with a digital non-mydriatic camera. (Proposed International Clinical Diabtetic Retinopathy and Diabetic Macular Edema disease severity scales)	Not Specified	CGM-derived metrics are significantly associated with DR

AUC_{IR} — area under curve in range; CGM — continuous glucose monitoring; CV — coefficient of variability; DR — diabetic retinopathy; HBGI — high blood glucose index; GMI — glucose management indicator; LBGI — low blood glucose index; MAGE — mean amplitude of glucose excursion; MODD — mean of daily differences; NDPR — non-proliferative diabetic retinopathy; PDR — proliferative diabetic retinopathy; PPDR — preproliferative diabetic retinopathy; SD — standard deviation; SDR — simple diabetic retinopathy; T2M — type 2 diabetes; TIR — time in range; VTDR — vision-threatening diabetic retinopathy.

personalized treatment plans, could help explain the direct impact of glycemic variability on DR outcomes. By monitoring changes in TIR alongside traditional markers like HbA1c, these studies can assess the efficacy of interventions in optimizing glycemic control and reducing the risk of DR development or progression. These insights can guide clinical strategies towards personalized medicine and precision healthcare, where treatment decisions are tailored to individual patient characteristics and metabolic profiles.

Conclusions

In conclusion, our study revealed that lower TIR is significantly associated with DR in T2D patients. Additionally, higher SD, MAGE, and CV were linked to the presence of DR. These findings emphasize the potential utility of these CGM-derived metrics in assessing and managing the risk of DR in individuals with T2D.

Article information

Supplementary materials

The Supplementary materials for this article can be found at https://journals.viamedica.pl/clinical_diabetology/article/view/99931.

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Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. ElSayed NA, Aleppo G, Aroda VR, et al. 6. Glycemic Targets: Standards of Care in Diabetes-2023. Diabetes Care. 2023; 46(Suppl 1): S97–S9S110, doi: 10.2337/dc23-S006, indexed in Pubmed: 36507646.
2. Beck RW, Connor CG, Mullen DM, et al. The Fallacy of Average: How Using HbA Alone to Assess Glycemic Control Can Be Misleading. Diabetes Care. 2017; 40(8): 994–999, doi: 10.2337/dc17-0636, indexed in Pubmed: 28733374.
3. Raj R, Mishra R, Jha N, et al. Time in range, as measured by continuous glucose monitor, as a predictor of microvascular complications in type 2 diabetes: a systematic review. BMJ Open Diabetes Res Care. 2022; 10(1), doi: 10.1136/bmjdrc-2021-002573, indexed in Pubmed: 34980591.
4. Kropp M, Golubnitschaja O, Mazurakova A, et al. Diabetic retinopathy as the leading cause of blindness and early predictor of cascading complications-risks and mitigation. EPMA J. 2023; 14(1): 21–42, doi: 10.1007/s13167-023-00314-8, indexed in Pubmed: 36866156.
5. Lee R, Wong TY, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. Eye Vis (Lond). 2015; 2: 17, doi: 10.1186/s40662-015-0026-2, indexed in Pubmed: 26605370.
6. GBD 2019 Blindness and Vision Impairment Collaborators, Vision Loss Expert Group of the Global Burden of Disease Study. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the Right to Sight: an analysis for the Global Burden of Disease Study. Lancet Glob Health. 2021; 9(2): e144–e160, doi: 10.1016/S2214-109X(20)30489-7, indexed in Pubmed: 33275949.
7. Teo ZL, Tham YC, Yu M, et al. Global Prevalence of Diabetic Retinopathy and Projection of Burden through 2045: Systematic Review and Meta-analysis. Ophthalmology. 2021; 128(11): 1580–1591, doi: 10.1016/j.ophtha.2021.04.027, indexed in Pubmed: 33940045.
8. Battelino T, Danne T, Bergenstal RM, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care. 2019; 42(8): 1593–1603, doi: 10.2337/dci19-0028, indexed in Pubmed: 31177185.
9. Chehregosha H, Khamseh ME, Malek M, et al. A View Beyond HbA1c: Role of Continuous Glucose Monitoring. Diabetes Ther. 2019; 10(3): 853–863, doi: 10.1007/s13300-019-0619-1, indexed in Pubmed: 31037553.
10. Freckmann G. Basics and use of continuous glucose monitoring (CGM) in diabetes therapy. Journal of Laboratory Medicine. 2020; 44(2): 71–79, doi: 10.1515/labmed-2019-0189.
11. Zhou Z, Sun B, Huang S, et al. Glycemic variability: adverse clinical outcomes and how to improve it? Cardiovasc Diabetol. 2020; 19(1): 102, doi: 10.1186/s12933-020-01085-6, indexed in Pubmed: 32622354.
12. Hirsch IB, Welsh JB, Calhoun P, et al. Associations between HbA and continuous glucose monitoring-derived glycaemic variables. Diabet Med. 2019; 36(12): 1637–1642, doi: 10.1111/dme.14065, indexed in Pubmed: 31267573.
13. Beck RW, Bergenstal RM, Riddlesworth TD, et al. Validation of Time in Range as an Outcome Measure for Diabetes Clinical Trials. Diabetes Care. 2019; 42(3): 400–405, doi: 10.2337/dc18-1444, indexed in Pubmed: 30352896.
14. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021; 372(71): 1–9, doi: 10.1136/bmj.n71.
15. Wells G, Shea B, O'Conell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, 2013. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (17.08.2023).
16. Hayashi A, Shimizu N, Suzuki A, et al. Novel clinical associations between time in range and microangiopathies in people with type 2 diabetes mellitus on hemodialysis. J Diabetes Complications. 2023; 37(5): 108470, doi: 10.1016/j.jdiacomp.2023.108470, indexed in Pubmed: 37043984.
17. Wang Y, Lu J, Shen Y, et al. Comparison of glucose time in range and area under curve in range in relation to risk of diabetic retinopathy in type 2 diabetes patients. J Diabetes Investig. 2022; 13(9): 1543–1550, doi: 10.1111/jdi.13811, indexed in Pubmed: 35435323.
18. Wakasugi S, Mita T, Katakami N, et al. Associations between continuous glucose monitoring-derived metrics and diabetic retinopathy and albuminuria in patients with type 2 diabetes. BMJ Open Diabetes Res Care. 2021; 9(1): e001923, doi: 10.1136/bmjdrc-2020-001923, indexed in Pubmed: 33879513.
19. Lu J, Ma X, Zhou J, et al. Association of Time in Range, as Assessed by Continuous Glucose Monitoring, With Diabetic Retinopathy in Type 2 Diabetes. Diabetes Care. 2018; 41(11): 2370–2376, doi: 10.2337/dc18-1131, indexed in Pubmed: 30201847.
20. Lu J, Ma X, Zhang L, et al. Glycemic variability assessed by continuous glucose monitoring and the risk of diabetic retinopathy in latent autoimmune diabetes of the adult and type 2 diabetes. J Diabetes Investig. 2019; 10(3): 753–759, doi: 10.1111/jdi.12957, indexed in Pubmed: 30306722.
21. American Diabetes Association Professional Practice Committee. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022; 45(Suppl 1): S83–S96, doi: 10.2337/dc22-S006, indexed in Pubmed: 34964868.
22. Danne T, Nimri R, Battelino T, et al. International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care.

2017; 40(12): 1631–1640, doi: 10.2337/dc17-1600, indexed in Pubmed: 29162583.
23. Mayeda L, Katz R, Ahmad I, et al. Glucose time in range and peripheral neuropathy in type 2 diabetes mellitus and chronic kidney disease. BMJ Open Diabetes Res Care. 2020; 8(1), doi: 10.1136/bmjdrc-2019-000991, indexed in Pubmed: 31958307.
24. Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA. 2006; 295(14): 1681–1687, doi: 10.1001/jama.295.14.1681, indexed in Pubmed: 16609090.
25. Maiorino MI, Signoriello S, Maio A, et al. Effects of Continuous Glucose Monitoring on Metrics of Glycemic Control in Diabetes: A Systematic Review With Meta-analysis of Randomized Controlled Trials. Diabetes Care. 2020; 43(5): 1146–1156, doi: 10.2337/dc19-1459, indexed in Pubmed: 32312858.
26. Yapanis M, James S, Craig ME, et al. Complications of Diabetes and Metrics of Glycemic Management Derived From Continuous Glucose Monitoring. J Clin Endocrinol Metab. 2022; 107(6): e2221–e2236, doi: 10.1210/clinem/dgac034, indexed in Pubmed: 35094087.
27. Hsu CR, Chen YT, Sheu WHH. Glycemic variability and diabetes retinopathy: a missing link. J Diabetes Complications. 2015; 29(2): 302–306, doi: 10.1016/j.jdiacomp.2014.11.013, indexed in Pubmed: 25534877.
28. Perais J, Agarwal R, Evans JR, et al. Prognostic factors for the development and progression of proliferative diabetic retinopathy in people with diabetic retinopathy. Cochrane Database Syst Rev. 2023; 2(2): CD013775, doi: 10.1002/14651858.CD013775.pub2, indexed in Pubmed: 36815723.
29. Tarasewicz D, Conell C, Gilliam LK, et al. Quantification of risk factors for diabetic retinopathy progression. Acta Diabetol. 2023; 60(3): 363–369, doi: 10.1007/s00592-022-02007-6, indexed in Pubmed: 36527502.
30. Chen DJ, Kuo JC, Wright AJ, et al. Determining Risk Factors That Affect Progression in Patients with Nonproliferative Diabetic Retinopathy. J Ophthalmol. 2021; 2021: 6064525, doi: 10.1155/2021/6064525, indexed in Pubmed: 34888097.
31. Tsujimoto T, Kajio H. Four-Year Screening Interval and Vision-Threatening Retinopathy in Type 2 Diabetes Patients With Good Glycemic Control. Mayo Clin Proc. 2021; 96(2): 322–331, doi: 10.1016/j.mayocp.2020.07.031, indexed in Pubmed: 33549254.
32. Yoo JH, Choi MS, Ahn J, et al. Association Between Continuous Glucose Monitoring-Derived Time in Range, Other Core Metrics, and Albuminuria in Type 2 Diabetes. Diabetes Technol Ther. 2020; 22(10): 768–776, doi: 10.1089/dia.2019.0499, indexed in Pubmed: 32167394.
33. Kim MY, Kim G, Park JiY, et al. The Association Between Continuous Glucose Monitoring-Derived Metrics and Cardiovascular Autonomic Neuropathy in Outpatients with Type 2 Diabetes. Diabetes Technol Ther. 2021; 23(6): 434–442, doi: 10.1089/dia.2020.0599, indexed in Pubmed: 33523771.