JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Comparison of glucose time in range and area under curve in range in relation to risk of diabetic retinopathy in type 2 diabetes patients

Yaxin Wang, Jingyi Lu, Yun Shen, Jiaying Ni, Lei Zhang, Wei Lu, Wei Zhu, Yuqian Bao, Jian Zhou*

Shanghai Key Laboratory of Diabetes Mellitus, Shanghai Clinical Center for Diabetes, Shanghai Diabetes Institute, Department of Endocrinology and Metabolism, Shanghai Jiao Tong University School of Medicine Affiliated Sixth People's Hospital, Shanghai, China

Keywords
Area under the curve in range, Continuous glucose monitoring, Time in range

***Correspondence**
Jian Zhou
Tel.: +86-21-6436-9181
Fax: +86-21-6436-8031
E-mail address:
zhoujian@sjtu.edu.cn

J Diabetes Investig 2022; 13: 1543–1550

doi: 10.1111/jdi.13811

ABSTRACT

Aims/introduction: We proposed a novel continuous glucose monitoring (CGM)-based metric, area under the curve in range (AucIR), for integrating both the amplitude and duration of dysglycemia, and further compared AucIR with the emerging key CGM-derived metric, time in range (TIR).

Materials and methods: A total of 2,030 adult patients with type 2 diabetes were enrolled during May 2020 to October 2021. AucIR and TIR were measured with 7-day CGM data. Logistic regression analysis and the *C*-statistic was carried out to assess the association of AucIR and TIR with diabetic retinopathy (DR).

Results: Both AucIR (r = –0.89) and TIR (r = –0.95) were strongly correlated with mean glucose levels. Compared with TIR, AucIR showed a tighter relationship with parameters of glycemic variability, including the coefficient of variation (r = –0.56), standard deviation (r = –0.89) and mean amplitude of glycemic excursions (r = –0.70). For each absolute 10% decrease in AucIR, the risk of DR was increased by 7% (95% confidence interval 1.02–1.13) after adjustment for confounders. With respect to TIR, each absolute 10% decrease was associated with an 8% (95% confidence interval 1.03–1.14) increased risk of DR. The model discrimination for DR, as measured by *C*-statistic, did not differ significantly between the two metrics (P > 0.05).

Conclusions: AucIR did not provide added benefit over TIR in the assessment of DR risk among patients with type 2 diabetes. The potential value of AucIR needs to be explored in future studies.

INTRODUCTION

With the constant advances in technology, continuous glucose monitoring (CGM) has become more widely adopted for diabetes management. However, interpretation of huge amounts of glucose data generated by CGM technology remains a key issue. Among the standardized CGM metrics recommended by international consensus statements and guidelines[1–3], time in range (TIR) has been popularized as an intuitive and valid measure of glucose control. Emerging evidence shows that lower TIR is significantly associated with increased risk of diabetes-related outcomes[4–9], including our previous study correlating 3-day TIR with varying degrees of diabetic retinopathy (DR) in type 2 diabetes[10]. However, it should be recognized that TIR does not reflect the amplitude of glucose excursions, as it is calculated as the time spent in a target glucose range (Figure 1a).

Needless to say, the amplitude of hyperglycemia/hypoglycemia is significantly correlated with the clinical outcomes of diabetes. For example, all-cause mortality increased significantly with increasing average glucose levels reflected by glycated hemoglobin A1c in the combined Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort[11], and severe hypoglycemia was also linked to cardiovascular and all-cause mortality[12,13]. In concert with this notion, a previous longitudinal study showed that the area under the curve (AUC; >10 mmol/L) was significantly related to the risk of retinopathy

Received 16 March 2022; revised 7 April 2022; accepted 13 April 2022

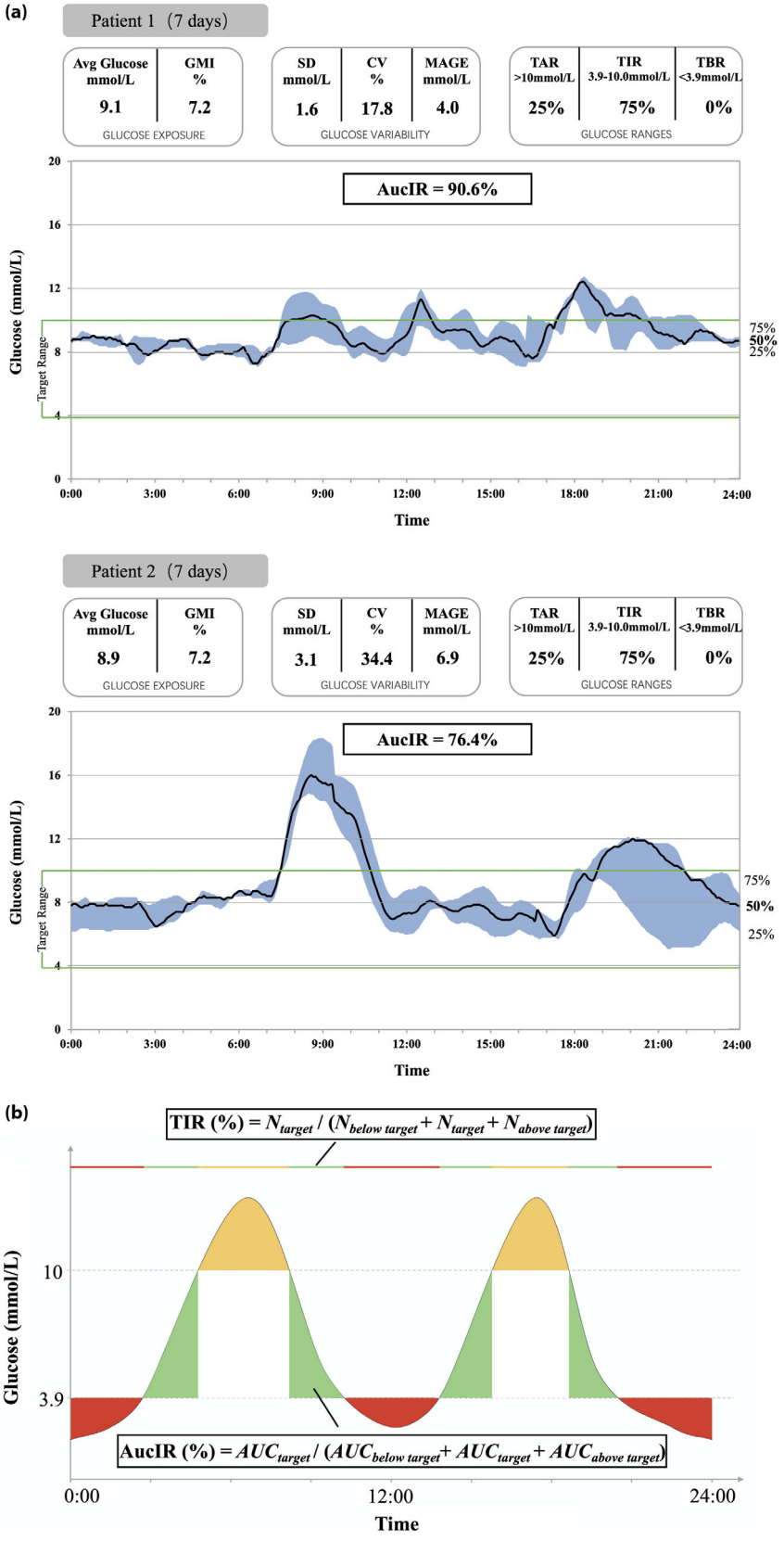

Figure 1 | (a) Ambulatory glucose profiles from two typical inpatients with type 2 diabetes. Although the two patients had identical time in range (TIR; 75%) that met the target, the amplitudes of glucose excursions varied greatly, which would lead to different management suggestion for lifestyle changes or antihyperglycemic therapy adjustments. This is where area under the curve (AUC) in range (AucIR) has considerable benefit. As shown in this figure, patient 2 (76.4%) with higher postprandial glucose levels had markedly lower AucIR than patient 1 (90.6%). (b) Graphical representation of AucIR. AucIR is defined as the average percentage of AUC for glucose between 3.9 mmoL/L and 10.0 mmoL/L (green area), in the sum of AUC above (yellow area), between (green area) and below (red area) these thresholds during a 24-h period. CV, coefficient of variation; GMI, glucose management indicator; MAGE, mean amplitude of glycemic excursions; SD, standard deviation; TAR, time above range; TBR, time below range.

progression and microalbuminuria development[4]. Furthermore, in the 2017 Advanced Technologies & Treatments for Diabetes consensus conference, AUC was recommended as one of the core CGM metrics for assessing glucose control, and should be documented in the standardized CGM reports – Ambulatory Glucose Profile[1]. Taken together, a new glucose metric that captures both the duration and amplitude of dysglycemia might theoretically provide additional information over TIR. Therefore, based on the definition of TIR and AUC, we developed a novel CGM-based metric, area under the curve in range (AucIR), which is defined as the average percentage of AUC for glucose between 3.9 and 10.0 mmoL/L, in the sum of AUC above, between and below these thresholds during a 24-h period (Figure 1b). For further comparison of the clinical utility between AucIR and TIR, we assessed the correlations among AucIR, TIR and other CGM metrics, and the relationships of the two metrics to DR.

MATERIALS AND METHODS

Study population

In the present cross-sectional study, individuals who were admitted to the Department of Endocrinology and Metabolism of Shanghai Jiao Tong University School of Medicine Affiliated Sixth People's Hospital, Shanghai, China, were consecutively screened from May 2020 to October 2021. Patients with the diagnosis of type 2 diabetes aged between 18 and 80 years and with complete CGM data were eligible for the study. We excluded those with diabetic ketoacidosis; severe and recurrent hypoglycemic events; and acute infection, chemotherapy and use of corticosteroids within the previous 3 months. Finally, a total of 2,030 patients were included in the analysis. The study was approved by the Research Ethics Committees of Shanghai Jiao Tong University School of Medicine Affiliated Sixth People's Hospital, and was carried out in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

Clinical and biological parameters

Sex, age, the duration of diagnosed diabetes, history of comorbidities, smoking and drinking status, and current use of medication were recorded through a standardized electronic health record form. All participants underwent a physical examination, including blood pressure, height and weight measurement ,as previously described[10]. Body mass index was calculated as weight (kg) divided by the square of height (m). All participants were fasted overnight for 10 h before venous blood sampling on day 2 of hospital admission. Biochemical measures, including fasting plasma glucose, fasting C-peptide, glycated hemoglobin A1c, total cholesterol, triglycerides, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol, were assayed as previously described[10].

CGM parameters

Retrospective CGM systems (iPro 2; Medtronic Inc, Northridge, CA, USA) were used for subcutaneous interstitial glucose monitoring. All participants had the sensor inserted (Enlite; Medtronic Inc) on the first day of hospital admission and removed after 7 days, generating a daily record of 288 glucose values. At least four capillary blood glucose levels per day were measured using SureStep blood glucose meter (LifeScan, Milpitas, CA, USA) to calibrate the CGM systems. AUC for glucose >10.0 mmol/L, between 3.9 and 10.0 mmol/L, and <3.9 mmol/L were calculated according to the trapezoidal rule. AucIR was defined as the average percentage of AUC for glucose between 3.9 and 10.0 mmol/L, in the sum of AUC above, between and below these thresholds during a 24-h period (Figure 1b). TIR was defined as the average percentage of time for glucose between 3.9 and 10 mmol/L during a 24-h period. Glucose management indicator was calculated from the mean sensor glucose by the equation: glucose management indicator (%) = 3.31 + 0.023923 × mean glucose (mg/dL)[14]. Within-day glycemic variability metrics including coefficient of variation, standard deviation (SD) and mean amplitude of glycemic excursions were also calculated. High blood glucose index and low blood glucose index were calculated to reflect the risk of hyperglycemia and hypoglycemia, respectively[15].

Assessment of DR

Non-mydriatic digital fundus photography was carried out with a 45°, 6.3-megapixel camera (CR6-45NM; Canon, Lake Success, NY, USA) for the screening of DR by a trained ophthalmologist. Participants were promptly referred to an experienced ophthalmologist for further examinations and diagnosis if photographs were uninterpretable or DR was observed on screening. DR was diagnosed and graded by severity according to the International Classification of Diabetic Retinopathy[16], as previously described[10].

Statistical analysis

R version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria) was used for the statistical analysis. Continuous variables with a normal or non-normal distribution are presented as the mean ± SD or median with interquartile range (25–75%), respectively, and categorical variables as percentages (%). Characteristics of participants were compared between groups by using unpaired Student's *t* tests or Wilcoxon rank sum tests for continuous variables, and χ^2-tests for categorical variables.

Spearman correlation coefficients (*r*) were calculated to assess the correlations among CGM parameters. The correlations and distributions of those parameters are shown in matrix form[17]. Restricted cubic splines nested in logistic models were used to test the linear association of AucIR and TIR with the risk of DR. Binary and multinomial logistic regression analysis was carried out to assess the relationship of AucIR, as either categorical (quartile 4 [Q4] as the reference group: >92.8%, quartile 3 [Q3]: 81.8~92.8%, quartile 2 [Q2]: 65.2~81.7% and quartile 1 [Q1]: ≤65.1%) or continuous variables (each absolute 10% decrease), with DR presence as the primary outcome and DR severity as the secondary outcome. Similarly, the relationship of TIR with the presence and severity of DR was also assessed using binary and multinomial logistic regression analysis. The *C*-statistic, integrated discrimination improvement and net reclassification improvement indexes were calculated to compare the discrimination ability of AucIR with TIR in identifying DR, as assessed by using fully adjusted logistic models.

RESULTS

The characteristics of the enrolled 2,030 participants (1,255 men and 775 women) are summarized in Table 1. The median age was 61.0 years (53.0–68.0 years), and median diabetes duration was 12.0 years (5.0–19.0 years). A total of 551 participants were diagnosed with DR, equivalent to 27.1% of all participants. The median AucIR was 77.8% (59.3–91.1%) in participants with DR compared with 82.7% (67.5–93.6%) in those without DR ($P < 0.001$). Meanwhile, median TIR was 69.0% (52.0–82.0%) in participants with DR compared with 74.0% (60.0–86.0%) in those without DR ($P < 0.001$).

The distributions of CGM metrics and correlations among them are shown in Figure 2. Both AucIR ($r = -0.89$,

Table 1 | Clinical characteristics of participants by the presence of diabetic retinopathy

	Total (*n* = 2,030)	Without DR (*n* = 1,479)	With DR (*n* = 551)	*P*-value
Female	775 (38.2)	553 (37.4)	222 (40.3)	0.25
Age (years)	61.0 (53.0, 68.0)	61.0 (52.0, 68.0)	62.0 (55.0, 67.5)	0.12
Diabetes duration (years)	12.0 (5.0, 19.0)	10.0 (4.0, 17.0)	15.0 (10.0, 20.0)	<0.001
Systolic blood pressure (mmHg)	134.1 ± 17.1	132.4 ± 16.1	138.6 ± 19.0	<0.001
Diastolic blood pressure (mmHg)	80.7 ± 10.4	80.5 ± 10.2	81.2 ± 10.9	0.17
BMI (kg/m^2)	25.0 ± 3.7	25.1 ± 3.8	24.9 ± 3.4	0.20
Total cholesterol (mmol/L)	4.6 (3.7, 5.4)	4.6 (3.8, 5.4)	4.5 (3.7, 5.4)	0.45
Triglycerides (mmol/L)	1.4 (0.9, 2.1)	1.4 (1.0, 2.1)	1.4 (0.9, 2.2)	0.84
HDL-C (mmol/L)	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)	0.31
LDL-C (mmol/L)	2.6 (2.0, 3.2)	2.6 (2.0, 3.2)	2.5 (1.9, 3.1)	0.008
HbA_{1c} (%)	8.4 (7.2, 9.9)	8.3 (7.1, 9.8)	8.6 (7.3, 9.9)	0.03
HbA_{1c} (mmol/mol)	68 (55, 85)	67 (54, 84)	70 (56, 85)	0.03
GA (%)	20.7 (17.0, 25.8)	20.4 (16.8, 25.5)	21.5 (17.6, 26.6)	0.005
Fasting plasma glucose (mmol/L)	6.7 (5.6, 8.2)	6.8 (5.7, 8.2)	6.5 (5.5, 8.3)	0.18
Fasting C-peptide (ng/mL)	1.6 (1.1, 2.5)	1.8 (1.1, 2.5)	1.5 (1.0, 2.2)	<0.001
CGM metrics				
GMI (%)	7.1 (6.7, 7.6)	7.1 (6.7, 7.5)	7.2 (6.8, 7.7)	<0.001
Coefficient of variation (%)	27.0 (22.6, 32.1)	26.6 (22.4, 31.7)	27.9 (23.7, 32.6)	0.001
Standard deviation (mmol/L)	2.4 (1.9, 3.0)	2.4 (1.8, 3.0)	2.6 (2.0, 3.2)	<0.001
TIR (%)	73.0 (58.0, 85.0)	74.0 (60.0, 86.0)	69.0 (52.0, 82.0)	<0.001
AucIR (%)	81.7 (65.1, 92.8)	82.7 (67.5, 93.6)	77.8 (59.3, 91.1)	<0.001
Current smoker	442 (21.8)	328 (22.2)	114 (20.7)	0.51
Current alcohol drinker	307 (15.1)	222 (15.0)	85 (15.4)	0.87
Anti-diabetic agents				
Oral antidiabetes drugs	1,314 (64.7)	970 (65.6)	344 (62.4)	0.20
Insulin	1,467 (72.3)	1,016 (68.7)	451 (81.9)	<0.001
Antihypertension agents	1,084 (53.4)	754 (51.0)	330 (59.9)	<0.001
Lipid-lowering agents	1,555 (76.6)	1,126 (76.1)	429 (77.9)	0.45

Data are expressed as the mean ± standard deviation, median (interquartile range 25–75%) or *n* (%). AucIR, area under the curve in range; BMI, body mass index; CGM, continuous glucose monitoring; GA, glycated albumin; GMI: glucose management indicator; HbA_{1c}, glycated hemoglobin A_{1c}; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TIR, time in range.

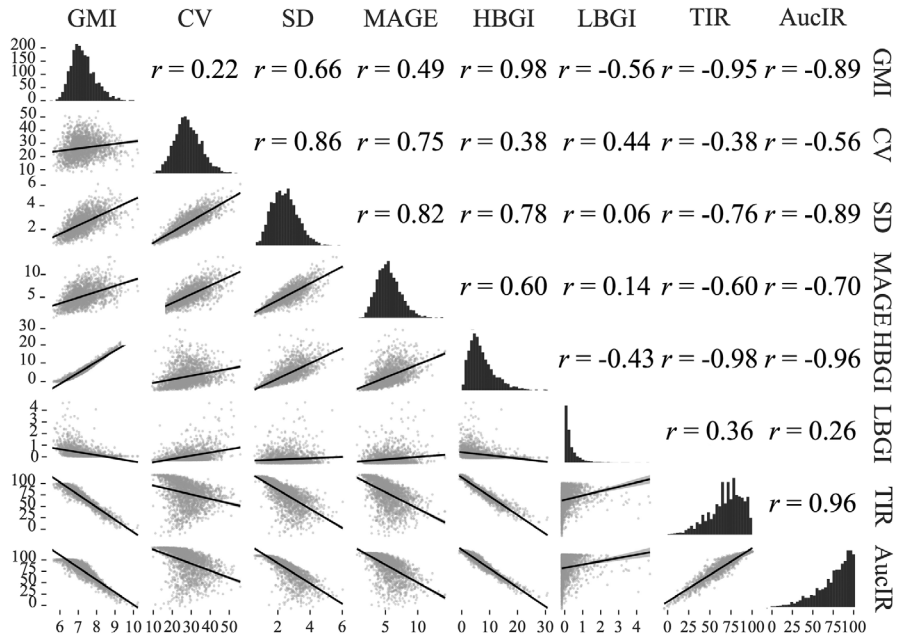

Figure 2 | The distributions of continuous glucose monitoring (CGM) metrics and correlations among them. The distributions of CGM metrics are shown in the diagonal area. Correlations among area under the curve in range (AucIR), time in range (TIR) and selected CGM metrics are shown in the upper area. All *r* values are Spearman's correlation coefficients with $P < 0.001$. Scatter plots for paired AucIR, TIR and selected CGM metrics values are shown in the lower area. CV, coefficient of variation; GMI, glucose management indicator; HBGI, high blood glucose index; LBGI, low blood glucose index MAGE, mean amplitude of glycemic excursions; SD, standard deviation.

$P < 0.001$) and TIR ($r = -0.95$, $P < 0.001$) had strongly negative correlations with glucose management indicator. Meanwhile, there were significant correlations between AucIR and parameters of glycemic variability, including coefficient of variation ($r = -0.56$), SD ($r = -0.89$) and mean amplitude of glycemic excursions ($r = -0.70$; all $P < 0.001$). However, the correlations were weaker for TIR with coefficient of variation ($r = -0.38$), SD ($r = -0.76$) and mean amplitude of glycemic excursions ($r = -0.60$; all $P < 0.001$).

Restricted cubic spline analysis suggested a significantly linear and inverse relationship between AucIR and the risk of DR (P for non-linear = 0.92; Figure S1a). Multivariable-adjusted (age, sex, current smoking status, diabetes duration, body mass index, systolic blood pressure, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol) odds ratios (ORs) for DR across descending quartiles of AucIR were 1.00, 1.07 (95% confidence interval [CI] 0.79–1.45), 1.19 (95% CI 0.88–1.60) and 1.40 (95% CI 1.04–1.89; P for trend = 0.02), respectively. For each absolute 10% decrease in AucIR, the risk of DR was increased by 7% (95% CI 1.02–1.13) after adjustment for confounders. With respect to TIR, each absolute 10% decrease was associated with an 8% (95% CI 1.03–1.14) increased risk of DR (Table 2).

Table 2 | Odd ratios for diabetic retinopathy according to area under the curve in range and time in range

	Quartiles				*P*-value for trend	each absolute 10% decrease
	Q4	Q3	Q2	Q1		
AucIR	>92.8%	81.8–92.8%	65.2–81.7%	≤65.1%		
Model 1	1.00	1.20 (0.90–1.61)	1.38 (1.04–1.84)	1.77 (1.34–2.35)	<0.001	1.12 (1.07–1.17)
Model 2	1.00	1.07 (0.79–1.45)	1.19 (0.88–1.60)	1.40 (1.04–1.89)	0.02	1.07 (1.02–1.13)
TIR	>85%	74–85%	59–73%	≤58%		
Model 1	1.00	1.16 (0.86–1.56)	1.46 (1.10–1.95)	1.76 (1.32–2.34)	<0.001	1.13 (1.07–1.18)
Model 2	1.00	1.03 (0.75–1.41)	1.23 (0.91–1.67)	1.37 (1.01–1.86)	0.02	1.08 (1.03–1.14)

Model 1 was adjusted for age and sex; model 2 was adjusted for the covariates in model 1 plus current smoking status, diabetes duration, body mass index, systolic blood pressure, triglycerides, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol. AucIR, area under curve in range; TIR, time in range.

In a multinomial logistic regression model with participants without DR as the reference group, lower levels of AucIR were significantly associated with an increased risk of mild NPDR (OR 1.09, 95% CI 1.03–1.15; Table S1). A similar significant association was observed between TIR and the risk of mild NPDR (OR 1.09, 95% CI 1.03–1.16; Table S2). However, neither AucIR nor TIR was associated with moderate NPDR or vision-threatening DR.

The *C*-statistic values of the two models incorporating AucIR (0.6818, 95% CI 0.6559–0.7078) or TIR (0.6824, 95% CI 0.6566–0.7082) for DR identification did not differ significantly ($P = 0.64$). The integrated discrimination improvement (−0.0002, 95% CI −0.0011 to 0.0008, $P = 0.75$) and net reclassification improvement (−0.0816, 95% CI −0.1794 to 0.0162, $P = 0.10$) analyses were consistent with the *C*-statistic results, showing that compared with TIR, AucIR did not provide a significant improvement in risk discrimination (Table 3).

DISCUSSION

The current study proposed a novel CGM metric, AucIR, for assessing glucose control. We found that, in addition to the strong correlations with mean glucose levels for both AucIR and TIR, the former seemed to show a tighter relationship with parameters of glycemic variability than the latter. This observation can be explained by the inherent feature of AUC, which integrates both the amplitude and duration of glucose excursions. Figure 1a shows the representative CGM data for two patients with type 2 diabetes. Although the two patients had identical TIR values, the amplitudes of glucose excursions varied greatly, accompanied by remarkably different values of AucIR. Therefore, AucIR seems to provide more information on the quality of glucose control.

There is emerging evidence supporting associations of TIR with diabetes-related complications, including diabetic retinopathy[4,10], albuminuria[4,18], cardiovascular autonomic neuropathy[5], peripheral neuropathy[6], and all-cause and cardiovascular mortality[8]. Meanwhile, apart from data obtained in inpatients settings, several studies in outpatients also showed that lower levels of TIR were closely related to an increased risk of diabetic complications[19,20]. In this context, the new guideline of American Diabetes Association placed TIR among glucose targets with comprehensive and detailed recommendations[3]. Regarding AucIR, although it has not been discussed previously, associations of AUC (>10 mmol/L) with the risk of retinopathy progression and microalbuminuria development was reported in a post-hoc analysis of the Diabetes Control and Complications Trial[4]. Based on 7-day CGM data, the present study found that AucIR was significantly associated with the risk of DR, although it did not provide superior model discrimination over TIR. The present results in turn suggest that TIR, which only considers the duration of dysglycemia, might be sufficient for risk prediction of DR. Nevertheless, it is noteworthy that AucIR in the current study mostly reflected information on hyperglycemia due to the extremely short time spent in hypoglycemia among the enrolled patients with type 2 diabetes, which could underestimate the value of AucIR in the assessment of overall glucose control. Therefore, it might be interesting to evaluate the performance of AucIR in patients with a higher risk of hypoglycemia, such as type 1 diabetes patients. Additionally, the potential added benefit of AucIR needs to be further examined using other outcomes, such as nephropathy and cardiovascular events.

The major strengths of the present study include well-documented clinical traits and relatively large sample size. However, there are still certain limitations that should be clarified. First, the present results are based on a cross-sectional study design, which cannot establish a cause-and-effect relationship between AucIR and the risk of DR. Second, as shown in previous studies, the optimal sampling duration for CGM to determine 3-month glucose control is 14 days[21,22]. Therefore, the CGM duration of 7 days used in the current study might not be long enough to optimally assess the overall glycemic pattern. Finally, CGM data were obtained in the inpatient settings, which might not fully represent their historical glycemic control in ordinary daily life. In addition, the participants enrolled in the present study were all Chinese with type 2 diabetes exclusively. Thus, whether the present results can be generalized to other populations with diabetes needs to be further explored.

In conclusion, among type 2 diabetes, although AucIR is strongly correlated with mean glucose levels and superior to TIR in correlations with parameters of glycemic variability, there is no significant difference in their associations with DR. Therefore, as a simple measure, TIR might be sufficient for risk prediction of DR in type 2 diabetes patients. Longitudinal studies with different populations and outcomes design are

Table 3 | Comparison of prediction performance between area under curve in range and time in range in the risk of diabetic retinopathy

	Basic model + TIR	Basic model + AucIR	*P*-value
C-statistic (95% CI)	0.6824 (0.6566–0.7082)	0.6818 (0.6559–0.7078)	0.64
IDI (95% CI)	Ref.	−0.0002 (−0.0011 to 0.0008)	0.75
Continuous NRI (95% CI)	Ref.	−0.0816 (−0.1794 to 0.0162)	0.10

The basic model included age, sex, current smoking status, diabetes duration, body mass index, systolic blood pressure, triglycerides, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol. AucIR, area under curve in range; IDI, integrated discrimination improvement; NRI, net reclassification improvement; TIR, time in range.

warranted to further explore whether AucIR has added value over TIR in predicting diabetes-related outcomes.

ACKNOWLEDGMENTS

This work was funded by the National Key Research and Development Program of China (2018YFC2001004), the Shanghai Municipal Education Commission-Gaofeng Clinical Medicine Grant (20161430) and the Shanghai "Rising Stars of Medical Talent" Youth Development Program–Outstanding Youth Medical Talents. The authors thank the fund, and all patients, research staff and students who participated in this work.

DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: The study was approved by the Research Ethics Committees of Shanghai Jiao Tong University School of Medicine Affiliated Sixth People's Hospital, and carried out in accordance with the Declaration of Helsinki.

Informed consent: Informed consent was obtained from all participants.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

REFERENCES

1. Danne T, Nimri R, Battelino T, *et al*. International consensus on use of continuous glucose monitoring. *Diabetes Care* 2017; 40: 1631–1640.
2. Grunberger G, Sherr J, Allende M, *et al*. American Association of Clinical Endocrinology clinical practice guideline: the use of advanced technology in the management of persons with diabetes mellitus. *Endocr Pract* 2021; 27: 505–537.
3. Committee ADAPP. 6. Glycemic targets: standards of medical care in diabetes—2022. *Diabetes Care* 2021; 45 (Supplement_1): S83–S96.
4. 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: 400–405.
5. Guo Q, Zang P, Xu S, *et al*. Time in range, as a novel metric of glycemic control, is reversely associated with presence of diabetic cardiovascular autonomic neuropathy independent of HbA1c in Chinese type 2 diabetes. *J Diabetes Res* 2020; 2020: 5817074.
6. 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: e000991.
7. Lu J, Home PD, Zhou J. Comparison of multiple cut points for time in range in relation to risk of abnormal carotid intima-media thickness and diabetic retinopathy. *Diabetes Care* 2020; 43: e99–e101.
8. Lu J, Wang C, Shen Y, *et al*. Time in range in relation to all-cause and cardiovascular mortality in patients with type 2 diabetes: a prospective cohort study. *Diabetes Care* 2021; 44: 549–555.
9. El Malahi A, Van Elsen M, Charleer S, *et al*. Relationship between time in range, glycemic variability, HbA1c and complications in adults with type 1 diabetes mellitus. *J Clin Endocrinol Metab* 2021; 107: e570–e581.
10. 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: 2370–2376.
11. Diabetes Control and Complications Trial (DCCT)/ Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Mortality in type 1 diabetes in the DCCT/EDIC versus the general population. *Diabetes Care* 2016; 39: 1378–1383.
12. Lee AK, Warren B, Lee CJ, *et al*. The association of severe hypoglycemia with incident cardiovascular events and mortality in adults with type 2 diabetes. *Diabetes Care* 2018; 41: 104–111.
13. Davis SN, Duckworth W, Emanuele N, *et al*. Effects of severe hypoglycemia on cardiovascular outcomes and death in the veterans affairs diabetes trial. *Diabetes Care* 2019; 42: 157–163.
14. Bergenstal RM, Beck RW, Close KL, *et al*. Glucose management indicator (GMI): a new term for estimating A1C from continuous glucose monitoring. *Diabetes Care* 2018; 41: 2275–2280.
15. Kovatchev BP. Metrics for glycaemic control – from HbA(1c) to continuous glucose monitoring. *Nat Rev Endocrinol* 2017; 13: 425–436.
16. Wilkinson CP, Ferris FL 3rd, Klein RE, *et al*. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology* 2003; 110: 1677–1682.
17. Varghese JS, Ho JC, Anjana RM, *et al*. Profiles of intraday glucose in type 2 diabetes and their association with complications: An analysis of continuous glucose monitoring data. *Diabetes Technol Ther* 2021; 23: 555–564.
18. 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: 768–776.
19. Kuroda N, Kusunoki Y, Osugi K, *et al*. Relationships between time in range, glycemic variability including hypoglycemia and types of diabetes therapy in Japanese patients with type 2 diabetes mellitus: Hyogo diabetes hypoglycemia cognition complications study. *J Diabetes Investig* 2021; 12: 244–253.
20. Kim MY, Kim G, Park JY, *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: 434–442.
21. Xing D, Kollman C, Beck RW, *et al*. Optimal sampling intervals to assess long-term glycemic control using continuous glucose monitoring. *Diabetes Technol Ther* 2011; 13: 351–358.

22. Riddlesworth TD, Beck RW, Gal RL, *et al*. Optimal sampling duration for continuous glucose monitoring to determine long-term glycemic control. *Diabetes Technol Ther* 2018; 20: 314–316.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1 Supporting information