Association of Time in Range, as Assessed by Continuous Glucose Monitoring, With Diabetic Retinopathy in Type 2 Diabetes

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OBJECTIVE

Continuous glucose monitoring (CGM) has provided new measures of glycemic control that link to diabetes complications. This study investigated the association between the time in range (TIR) assessed by CGM and diabetic retinopathy (DR).

RESEARCH DESIGN AND METHODS

A total of 3,262 patients with type 2 diabetes were recruited. TIR was defined as the percentage of time spent within the glucose range of 3.9–10.0 mmol/L during a 24-h period. Measures of glycemic variability (GV) were assessed as well. DR was determined by using fundus photography and graded as *1*) non-DR; *2*) mild nonproliferative DR (NPDR); *3*) moderate NPDR; or *4*) vision-threatening DR (VTDR).

RESULTS

The overall prevalence of DR was 23.9% (mild NPDR 10.9%, moderate NPDR 6.1%, VTDR 6.9%). Patients with more advanced DR had significantly less TIR and higher measures of GV (all *P* for trend <0.01). The prevalence of DR on the basis of severity decreased with ascending TIR quartiles (all *P* for trend <0.001), and the severity of DR was inversely correlated with TIR quartiles ($r = -0.147$; $P < 0.001$). Multinomial logistic regression revealed significant associations between TIR and all stages of DR (mild NPDR, $P = 0.018$; moderate NPDR, $P = 0.014$; VTDR, $P = 0.019$) after controlling for age, sex, BMI, diabetes duration, blood pressure, lipid profile, and HbA_{1c}. Further adjustment of GV metrics partially attenuated these associations, although the link between TIR and the presence of any DR remained significant.

CONCLUSIONS

TIR assessed by CGM is associated with DR in type 2 diabetes.

Continuous glucose monitoring (CGM) continuously captures the glucose profile over a number of days and may be the best way to identify an individual's current glycemic status. Increasing evidence shows that the use of CGM improves glycemic control, with an unchanged or even decreased risk of hypoglycemia (1–3). The introduction of CGM has provided an opportunity to develop metrics of glycemic control that provide valuable information beyond that furnished by glycated hemoglobin A_{1c} (HbA_{1c}). Among the metrics generated from CGM, time in range (TIR) refers to the time an individual spends within their target glucose range (usually 3.9–10.0 mmol/L), which provides valuable information about whether the frequency and duration of hypoglycemia or hyperglycemia improve over time. In addition, TIR

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measurements are useful for evaluating and comparing different glucose-lowering interventions (4–6). Therefore, it is not surprising that a recent consensus on CGM developed by an international group of experts recommended that TIRs be reported as key metrics of glycemic control in clinical trials (7). Despite the use of TIR in assessing glycemic control, the relation between TIR and diabetes complications remains unknown.

Diabetic retinopathy (DR) is one of the main microvascular complications of diabetes and is caused by long-term damage to the retinal microvasculature. Because the prevalence of diabetes is increasing worldwide, the number of patients with DR will continue to rise. DR can lead to severe, permanent visual impairment and is the most common cause of blindness in working-age adults (8). In the landmark Diabetes Control and Complications Trial (DCCT), the risk of DR was significantly higher in the conventional insulin treatment group than in the intensive insulin treatment group, even though these two groups had equivalent sustained levels of HbA_{1c}, a well-established DR risk factor (9). This finding raised the possibility that other measures of glycemic control beyond HbA_{1c} may relate to DR. Therefore the current study investigated the association of TIR obtained from CGM with the prevalence of DR in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study Population

A total of 3,262 patients with type 2 diabetes were consecutively recruited from among hospitalized patients at the Department of Endocrinology and Metabolism of the Shanghai Jiao Tong University Affiliated Sixth People's Hospital from January 2005 to the end of February 2012. Type 2 diabetes was diagnosed according to the 1999 World Health Organization criteria (10). Inclusion criteria were age ≥18 years, presence of type 2 diabetes, and a stable glucose-lowering regimen over the previous 3 months. Exclusion criteria included diabetic ketoacidosis; a hyperglycemic hyperosmolar state or severe and recurrent hypoglycemic events within the previous 3 months; and a history of malignancy, mental disorders, or severe kidney or liver dysfunction. The study protocol was approved by the ethics committees of Shanghai Jiao Tong University Affiliated Sixth People's Hospital in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from each participant.

CGM Parameters

A retrospective CGM system (Medtronic Inc., Northridge, CA) was used for subcutaneous interstitial glucose monitoring for three consecutive days. The sensor of the CGM system was inserted on day 0 and removed after 72 h, generating a daily record of 288 continuous sensor values. At least four capillary blood glucose readings per day were measured by using a SureStep blood glucose meter (LifeScan, Milpitas, CA) to calibrate the CGM system. After the 3-day monitoring period, TIR and glycemic variability (GV) metrics were calculated. TIR was defined as the percentage of time spent within the target glucose range of 3.9–10.0 mmol/L during a 24-h period. Intraday GV parameters included the SD of sensor glucose values, the glucose coefficient of variation (CV), and the mean amplitude of glycemic excursions (MAGE). CV was calculated by dividing the SD by the mean of the corresponding glucose readings. MAGE was calculated by measuring the arithmetic mean of the differences between consecutive peaks and nadirs, and only excursions of more than one SD of the mean glycemic value were considered.

All participants adhered to the original therapy regimen during the 3-day CGM period, and they were instructed to adhere to a standard diet. This diet was designed to ensure a total daily caloric intake of 25 kcal/kg, with 55% of calories coming from carbohydrates, 17% from proteins, and 28% from fats. Written instructions were provided to achieve the appropriate caloric content and to guide consumption times, which included breakfast (20% of daily calories; 0630–0730 h), lunch (40% of daily calories; 1100–1200 h), and dinner (40% of daily calories; 1700–1800 h).

Anthropometric and Biochemical Measurements

Each patient underwent a physical examination that included measurements of height, weight, and blood pressure. BMI was calculated as weight (kilograms) divided by squared height (meters). Blood pressure was measured three times using a standard mercury sphygmomanometer, and the measurements were averaged. One day before the CGM monitoring period, a venous blood sample was drawn at 0600 h after a 10-h overnight fast. Triglycerides (TG), total cholesterol, HDL cholesterol (HDL-C), and LDL cholesterol (LDL-C) were determined by applying standard enzymatic methods using a biochemical analyzer (7600-120; Hitachi, Tokyo, Japan). Fasting plasma glucose levels were assayed by using the glucose oxidase method. HbA_{1c} was measured by using high-performance liquid chromatography with a VARIANT II Hemoglobin A_{1c} analyzer (Bio-Rad Laboratories, Hercules, CA).

Assessment of DR

Fundus photography was performed by an ophthalmologist, who was blinded to subject characteristics, using a 45°, 6.3-megapixel digital nonmydriatic camera (CR6-45NM; Canon, Lake Success, NY) following a standardized protocol at the Department of Ophthalmology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital. Retinopathy was graded according to the International Classification of Diabetic Retinopathy (11). The severity of DR was classified as *1*) non-DR; *2*) mild nonproliferative DR (NPDR); *3*) moderate NPDR; *4*) severe NPDR; and *5*) proliferative DR (PDR). Because of the limited number of study participants with PDR (n = 27), PDR was combined with severe NPDR; together these were defined as vision-threatening DR (VTDR). When binocular DR was present and unequal, we used the more advanced DR measurement for analyses. Patients with ungradable retinal fundus photographs of both eyes were excluded from the study.

Statistical Analyses

The trends of continuous variables across the various groups were assessed with the use of linear polynomial contrasts in ANOVA for normally distributed variables and the Jonckheere-Terpstra test for non–normally distributed data. We used the Cochran-Armitage trend test to examine trends of rates across groups. Status by severity of DR was treated as an ordinal categorical variable (0 = non-DR, 1 = mild NPDR, 2 = moderate NPDR, 3 = VTDR). The association between severity of DR and TIR quartiles was ascertained by using the Spearman correlation coefficient. Multinomial logistic regression analysis was performed to evaluate the independent association of TIR with different stages of DR (i.e., mild NPDR, moderate NPDR, and VTDR) after controlling for clinical risk factors including

age, sex, BMI, diabetes duration, HbA_{1c}, blood pressure, and lipid profile, as well as GV metrics when indicated. The independent association between TIR and the presence of any DR (yes vs. no) was tested by using binary logistic regression analysis. A P value <0.05 (two-tailed) was considered statistically significant. Statistical analyses were performed using SPSS software version 17.0 (SPSS Inc., Chicago, IL).

RESULTS

The clinical characteristics of the patients are shown in Table 1. The mean ± SD age of the enrolled participants was 60.4 ± 12.0 years; they had a mean ± SD diabetes duration of 8.1 ± 6.8 years and HbA_{1c} of 8.9 ± 2.2% (74.0 ± 24.0 mmol/mol). Of the 3,262 participants, 780 were affected by DR, resulting in an overall prevalence of 23.9%. The prevalences of mild NPDR, moderate NPDR, and VTDR were 10.9%, 6.1%, and 6.9%, respectively.

Patients with more severe DR had longer diabetes duration; higher systolic blood pressure, HDL-C, and HbA_{1c}; and lower TG and fasting C-peptide. They also were less likely to be treated with oral antidiabetes drugs and had higher propensity to receive insulin, renin-angiotensin-aldosterone system inhibitors, and calcium-channel blockers (Table 1). The details of oral antidiabetes drug use are presented in Supplementary Table 1. TIR and all of the GV measures including SD, CV, and MAGE differed significantly across the various groups (all P for trend <0.001). The characteristics of study participants categorized by diabetes duration (<5, 5–10, and ≥ 10 years) and stage of DR can be found in Supplementary Tables 2–4; significant differences in TIR existed among the different groups by DR status throughout the three categories of diabetes duration.

Next, all of the patients were stratified according to quartiles of TIR (quartile 1 [Q1]: ≤51%; quartile 2 [Q2]: 51–71%; quartile 3 [Q3]: 71–86%; quartile 4 [Q4]: >86%). Table 2 depicts the characteristics of subjects by TIR quartiles. In general, the prevalence of DR by severity decreased with ascending quartiles of TIR (all P for trend <0.001) (Fig. 1). For example, the prevalence of VTDR was 9.7% in Q1, 8.2% in Q2, 6.3% in Q3, and 3.5% in Q4. Spearman correlation analysis revealed a significant association between TIR quartile and the severity of DR ($r = -0.147$; $P < 0.001$).

In a multinomial logistic regression model with patients without DR as the reference group, significant associations existed between TIR and the prevalence of DR by severity (mild NPDR: $P = 0.018$; moderate NPDR: $P = 0.014$; VTDR: $P = 0.019$) after adjusting for age, sex, BMI, diabetes duration, HbA_{1c}, blood pressure, and lipid profile (Table 3). When TIR was included as a categorical variable (quartiles) in the multinomial logistic

Table 1—Characteristics of study participants by the presence and severity of DR

Variables	All subjects (n = 3,262)	No DR (n = 2,482)	Mild NPDR (n = 355)	Moderate NPDR (n = 198)	VTDR (n = 227)	P value for trend
Male sex	44.7	43.6	44.8	54.0	48.0	0.017
Age (years)	60.4 ± 12.0	60.2 ± 12.4	59.6 ± 11.0	61.2 ± 11.0	62.8 ± 9.8	0.142
Diabetes duration (years)	8.1 ± 6.8	7.2 ± 6.4	9.8 ± 6.8	11.7 ± 7.1	13.1 ± 7.1	<0.001
SBP (mmHg)	132.0 ± 17.5	130.6 ± 16.6	133.7 ± 18.0	136.2 ± 18.8	140.0 ± 21.7	<0.001
DBP (mmHg)	79.9 ± 9.6	79.7 ± 9.5	80.5 ± 9.2	80.1 ± 9.4	81.1 ± 11.0	0.061
BMI (kg/m^2)	25.1 ± 3.4	25.1 ± 3.4	25.1 ± 3.5	25.0 ± 3.7	24.7 ± 3.5	0.124
Total cholesterol (mmol/L)	4.7 ± 1.1	4.7 ± 1.1	4.7 ± 1.1	4.8 ± 1.3	4.9 ± 1.4	0.330
TG (mmol/L)	1.9 ± 1.8	1.9 ± 1.8	1.8 ± 1.5	1.7 ± 1.4	1.8 ± 1.9	<0.001
HDL-C (mmol/L)	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	0.002
LDL-C (mmol/L)	3.2 ± 1.0	3.1 ± 1.0	3.1 ± 0.9	3.2 ± 1.1	3.2 ± 1.1	0.980
HbA_{1c} (%)	8.9 ± 2.2	8.8 ± 2.2	9.0 ± 1.8	9.4 ± 2.0	9.4 ± 2.1	<0.001
HbA_{1c} (mmol/mol)	74.0 ± 24.0	73.0 ± 24.0	75.0 ± 19.7	79.0 ± 21.9	79.0 ± 23.0	
Fasting C-peptide (ng/mL)	1.9 ± 1.3	2.1 ± 1.3	1.8 ± 1.0	1.6 ± 1.0	1.4 ± 0.9	<0.001
SD (mmol/L)	2.3 ± 0.9	2.2 ± 0.9	2.3 ± 0.8	2.5 ± 0.9	2.6 ± 0.9	<0.001
CV (%)	25.6 ± 8.5	25.3 ± 8.4	25.5 ± 8.5	26.6 ± 9.2	28.0 ± 9.0	<0.001
MAGE (mmol/L)	5.8 ± 2.5	5.7 ± 2.5	6.0 ± 2.5	6.1 ± 2.4	6.5 ± 2.6	<0.001
TIR (%)	66.6 ± 23.5	68.4 ± 23.6	63.5 ± 24.2	57.8 ± 23.9	59.3 ± 22.6	<0.001
Current smoker	24.9	25.1	29.5	18.8	21.6	0.166
Use antidiabetes agents						
Oral antidiabetes drugs	64.0	65.7	65.2	51.8	55.2	<0.001
Insulin	68.4	64.0	75.9	83.1	91.9	<0.001
Use antihypertension agents						
RAAS inhibitors	42.8	41.4	41.3	46.7	57.2	<0.001
Calcium-channel blockers	18.9	18.3	18.3	22.3	23.4	0.033
β-Blockers	8.7	9.2	7.4	8.6	5.9	0.093
Diuretics	3.3	3.1	2.9	1.5	7.7	0.171
Use lipid-lowering agents						
Statins	24.5	23.5	28.9	28.4	24.8	0.128
Fibrates	10.0	10.5	8.6	10.2	7.2	0.119

Data are mean ± SD or percentage unless otherwise indicated. DBP, diastolic blood pressure; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure.

Table 2—Characteristics of study participants by quartiles of TIR

Variables	TIR quartiles Q1 (≤51%) (*n* = 812)	Q2 (51–71%) (*n* = 855)	Q3 (71–86%) (*n* = 791)	Q4 (>86%) (*n* = 804)	*P* value for trend
Male sex	49.3	44.2	41.7	43.6	0.016
Age (years)	61.2 ± 12.8	61.6 ± 11.7	60.1 ± 11.6	58.6 ± 11.7	0.929
Diabetes duration (years)	9.4 ± 7.1	8.7 ± 7.2	7.8 ± 6.3	6.6 ± 6.1	0.020
SBP (mmHg)	132.5 ± 18.3	132.5 ± 17.7	131.8 ± 16.9	131.1 ± 17.0	0.386
DBP (mmHg)	79.9 ± 10.1	79.8 ± 9.8	79.9 ± 8.9	80.1 ± 9.4	0.956
BMI (kg/m^2)	25.0 ± 3.4	24.6 ± 3.4	25.2 ± 3.5	25.4 ± 3.4	<0.001
Total cholesterol (mmol/L)	4.9 ± 1.3	4.7 ± 1.2	4.7 ± 1.0	4.6 ± 1.0	<0.001
TG (mmol/L)	2.1 ± 2.0	1.8 ± 1.9	1.9 ± 1.7	1.9 ± 1.5	<0.001
HDL-C (mmol/L)	1.1 ± 0.3	1.2 ± 0.4	1.1 ± 0.3	1.1 ± 0.3	0.005
LDL-C (mmol/L)	3.2 ± 1.0	3.2 ± 1.1	3.1 ± 0.9	3.1 ± 0.9	0.137
HbA_{1c} (%)	10.3 ± 1.9	9.4 ± 2.0	8.5 ± 2.0	7.4 ± 1.7	<0.001
HbA_{1c} (mmol/mol)	89.0 ± 20.8	79.0 ± 21.9	69.0 ± 21.9	57.0 ± 18.6	
Fasting C-peptide (ng/mL)	1.9 ± 1.7	1.7 ± 1.1	2.0 ± 1.2	2.2 ± 1.0	0.041
SD (mmol/L)	2.9 ± 0.9	2.7 ± 0.7	2.2 ± 0.5	1.4 ± 0.4	<0.001
CV (%)	25.3 ± 8.6	30.0 ± 8.7	27.1 ± 7.0	19.7 ± 5.9	<0.001
MAGE (mmol/L)	7.0 ± 2.6	7.1 ± 2.4	5.6 ± 1.7	3.6 ± 1.4	0.172
Current smoker	21.2	26.2	24.5	27.6	0.012
Use antidiabetes agents					
Oral antidiabetes drugs	50.9	57.2	70.3	79.2	<0.001
Insulin	87.0	81.4	62.3	40.5	<0.001
Use antihypertensive agents					
RAAS inhibitors	44.2	41.3	42.8	43.1	0.830
Calcium-channel blockers	19.7	16.2	20.6	19.2	0.608
β-Blockers	9.8	9.0	7.6	8.5	0.237
Diuretics	3.9	3.8	3.1	2.2	0.044
Use lipid-lowering agents					
Statins	24.8	24.3	23.1	25.7	0.833
Fibrates	11.0	8.5	10.0	10.7	0.885

Data are mean ± SD or percentage unless otherwise indicated. DBP, diastolic blood pressure; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure.

regression model, the highest TIR quartile was independently associated with all stages of DR, compared with the lowest quartile (mild NPDR: odds ratio [OR] 0.56, *P* = 0.010; moderate NPDR: OR 0.48, *P* = 0.009; VTDR: OR 0.53, *P* = 0.023) (Table 4). Further adjustment of SD, but not CV or MAGE, attenuated the association of TIR, as a continuous variable, with mild NPDR and VTDR (Table 3). The link between VTDR and TIR, as a categorical variable, did not reach statistical significance after controlling for SD and CV, but did for MAGE (Table 4). The significant effect of TIR on the presence of any DR remained even after adjusting for GV metrics (Tables 3 and 4).

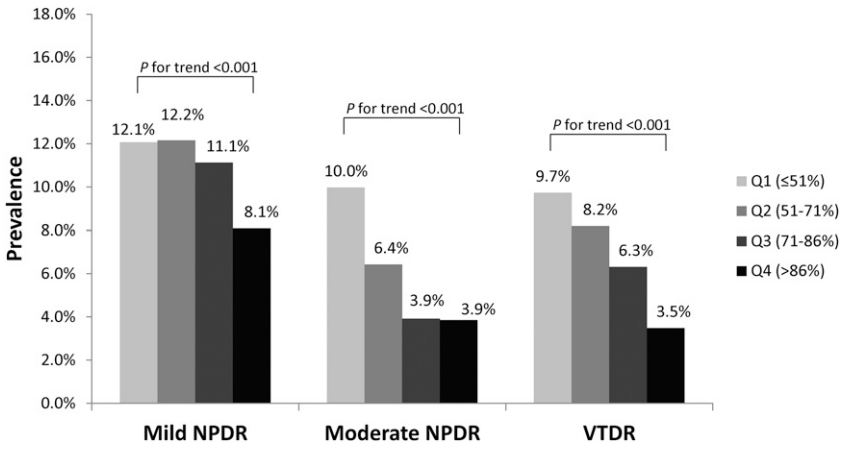

Figure 1—Prevalence of DR by severity, as a function of TIR quartile.

CONCLUSIONS

Among a population of 3,262 patients with diabetes, we observed an HbA_{1c}-independent association of TIR, assessed by using CGM, with the prevalence of all stages of DR. In addition, the measures indicating GV were significantly higher in patients with more advanced DR. When these GV metrics were considered, the relation remained between TIR and the presence of any DR, suggesting a GV-independent effect of TIR on DR.

HbA_{1c} is currently well established as the gold standard for assessment of glycemic control, and improvement of HbA_{1c} greatly reduces the risks of both macrovascular and microvascular complications in patients with type 1 and

Table 3—Associations between TIR and various stages of DR after controlling for confounding factors

	Mild NPDR		Moderate NPDR		VTDR		Any DR	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Model 1								
TIR*	0.93 (0.87–0.99)	0.018	0.91 (0.84–0.98)	0.014	0.91 (0.85–0.98)	0.019	0.92 (0.88–0.96)	<0.001
Model 2								
TIR*	0.94 (0.87–1.00)	0.054	0.91 (0.84–0.99)	0.025	0.95 (0.87–1.03)	0.186	0.93 (0.89–0.98)	0.006
SD	1.05 (0.87–1.26)	0.611	1.01 (0.81–1.26)	0.917	1.26 (1.02–1.55)	0.030	1.10 (0.96–1.25)	0.175
Model 3								
TIR*	0.93 (0.87–0.99)	0.020	0.91 (0.84–0.98)	0.014	0.91 (0.84–0.98)	0.017	0.92 (0.88–0.96)	<0.001
CV	1.01 (0.99–1.02)	0.462	1.01 (0.99–1.03)	0.588	1.02 (1.00–1.04)	0.021	1.01 (0.99–1.02)	0.084
Model 4								
TIR*	0.93 (0.87–0.99)	0.035	0.90 (0.83–0.97)	0.007	0.92 (0.85–0.99)	0.030	0.92 (0.88–0.96)	<0.001
MAGE	1.02 (0.96–1.08)	0.551	0.95 (0.88–1.02)	0.185	1.03 (0.96–1.10)	0.414	1.00 (0.96–1.05)	0.896

Model 1 was adjusted for age, sex, BMI, diabetes duration, blood pressure, lipid profile, and HbA_{1c}. Model 2 includes all variables in model 1 plus SD. Model 3 includes all variables in model 1 plus CV. Model 4 includes all variables in model 1 plus MAGE. *ORs and *P* values were estimated for each 10% increase in TIR (0–100%).

patients with type 2 diabetes (12,13). However, HbA_{1c} is unreliable in patients with anemia, hemoglobinopathies, or iron deficiency and in patients who are pregnant (7). Furthermore, evidence shows that HbA_{1c} differs among various ethnic groups (14,15), which affects the accuracy of HbA_{1c} measurements. It is notable that HbA_{1c} provides only an average glucose level over the previous 2–3 months and does not reflect individual patterns of glycemic control. Therefore, much effort has been dedicated to the search for glycemic measures beyond HbA_{1c} that can be used as surrogate markers of optimal glycemic control. In our study, TIR was significantly associated with the prevalence of all stages of DR even after adjusting for clinical risk factors, including HbA_{1c}; this suggests the value of TIR in assessing the risk of diabetes complications independent of HbA_{1c}. Moreover, Spearman correlation analysis implied that TIR was related to the severity of DR. Patients with similar HbA_{1c} values could have distinct glucose profiles. For instance, one patient could have long episodes of both hyperglycemia and hypoglycemia, whereas another could have a stable glucose pattern throughout the day. By contrast, TIR illustrates the time spent in the preferred glucose range, which is an intuitive way of assessing glycemic control, and it provides important information not captured by HbA_{1c}.

Table 4—Associations between quartiles of TIR and various stages of DR after controlling for confounding factors

	Mild NPDR		Moderate NPDR		VTDR		Any DR	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Model 1								
TIR Q4	0.56 (0.36–0.87)	0.010	0.48 (0.27–0.83)	0.009	0.53 (0.30–0.91)	0.023	0.53 (0.38–0.73)	<0.001
TIR Q3	0.83 (0.56–1.21)	0.323	0.49 (0.29–0.81)	0.006	0.64 (0.39–1.03)	0.064	0.67 (0.50–0.89)	0.006
TIR Q2	0.87 (0.61–1.24)	0.445	0.67 (0.44–1.03)	0.070	0.75 (0.50–1.14)	0.179	0.78 (0.60–1.01)	0.057
TIR Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Model 2								
TIR Q4	0.57 (0.34–0.94)	0.028	0.46 (0.24–0.86)	0.015	0.72 (0.38–1.37)	0.322	0.57 (0.39–0.83)	0.004
TIR Q3	0.83 (0.56–1.23)	0.356	0.48 (0.28–0.81)	0.006	0.75 (0.45–1.24)	0.257	0.70 (0.52–0.94)	0.019
TIR Q2	0.87 (0.61–1.24)	0.449	0.67 (0.44–1.03)	0.070	0.77 (0.51–1.16)	0.217	0.78 (0.60–1.01)	0.062
TIR Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
SD	1.01 (0.82–1.23)	0.955	0.96 (0.76–1.23)	0.766	1.26 (1.01–1.58)	0.042	1.07 (0.92–1.23)	0.382
Model 3								
TIR Q4	0.56 (0.36–0.88)	0.012	0.49 (0.28–0.86)	0.013	0.59 (0.34–1.04)	0.067	0.55 (0.40–0.76)	<0.001
TIR Q3	0.82 (0.56–1.21)	0.320	0.48 (0.29–0.80)	0.005	0.61 (0.38–0.98)	0.043	0.66 (0.49–0.88)	0.004
TIR Q2	0.87 (0.60–1.25)	0.442	0.65 (0.42–1.02)	0.061	0.68 (0.44–1.03)	0.071	0.75 (0.57–0.97)	0.032
TIR Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
CV	1.00 (0.98–1.02)	0.902	1.01 (0.98–1.03)	0.626	1.02 (1.01–1.04)	0.028	1.01 (1.00–1.02)	0.189
Model 4								
TIR Q4	0.56 (0.34–0.90)	0.016	0.40 (0.22–0.73)	0.003	0.52 (0.28–0.95)	0.034	0.50 (0.35–0.71)	<0.001
TIR Q3	0.83 (0.57–1.23)	0.353	0.46 (0.28–0.78)	0.004	0.66 (0.41–1.08)	0.097	0.67 (0.50–0.90)	0.007
TIR Q2	0.87 (0.61–1.25)	0.455	0.68 (0.44–1.05)	0.084	0.77 (0.51–1.16)	0.206	0.78 (0.60–1.02)	0.067
TIR Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
MAGE	1.00 (0.94–1.07)	0.890	0.93 (0.86–1.01)	0.096	1.02 (0.95–1.09)	0.616	0.99 (0.95–1.04)	0.678

Model 1 was adjusted for age, sex, BMI, diabetes duration, blood pressure, lipid profile, and HbA_{1c}. Model 2 includes all variables in model 1 plus SD; model 3 includes all variables in model 1 plus CV; model 4 includes all variables in model 1 plus MAGE.

On the other hand, it is obvious that TIR alone is not an adequate description of overall glycemic control. GV has recently attracted much attention as an independent predictor of diabetes complications (16). In vitro and in vivo studies demonstrated that GV could induce oxidative stress and endothelial dysfunction (17–19). In a similar way, GV has been linked to markers of oxidative stress in clinical studies (20–22), and several studies have reported associations of GV with cardiovascular outcomes and microvascular complications (23–26). GV metrics assessed by CGM were specifically associated with retinopathy, autonomic neuropathy, and cardiovascular events (26–28). Consistent with these observations, in our study all three measures of GV (i.e., SD, CV, and MAGE) deteriorated progressively with the worsening of DR, and we found independent associations of SD and CV with VTDR. It is notable that the adjustment for GV metrics, especially SD, to some extent attenuated the association of TIR with certain stages of DR. A possible explanation could be a moderate correlation between TIR and SD in our study samples ($r = -0.664$; $P < 0.001$; data not shown), which may cause multicollinearity in the regression model and thereby affect the results. Nevertheless, our study provides evidence of a GV-independent effect of TIR on the presence of any DR.

Considerable progress has been made in improving the accuracy and availability of, and reducing the cost of, CGM over the past 10–15 years. Translating our findings to the real world is now possible by performing diagnostic CGM evaluations in outpatients and using the data to make appropriate changes in therapy. For example, if a CGM evaluation shows that the primary pattern of dysglycemia is overnight or fasting hyperglycemia in contrast to postprandial hyperglycemia, the clinician may initiate or increase evening basal insulin rather than add a drug whose primary action is reduced meal-induced hyperglycemia, such as acarbose or a sodium–glucose cotransporter 2 inhibitor.

To date, few data are available regarding what TIR is achievable in patients with type 2 diabetes because CGM has not been routinely used. Studies have not reported TIR, or they have not been designed to use CGM to direct therapy changes. In the Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes (DIAMOND) trial, TIR was significantly improved (from 56% to 61%) in patients using multiple daily injections by adjusting insulin dosing on the basis of real-time CGM (29). However, patients using flash glucose monitoring alone were unable to achieve any improvement in TIR above the baseline of 58% (30). Patients with type 1 diabetes can now achieve TIR >70% by using advanced diabetes technologies such as the Medtronic MiniMed 670G Insulin Pump System (31). With further advances in insulin-delivery algorithms, fast-acting insulins, and the use of contextual data such as exercise and meal size, patients with type 1 diabetes may be able to achieve a TIR over 80%.

To the best of our knowledge, this is the first study to evaluate the association between CGM-assessed TIR and the risk of DR. The main strengths of this study include a large sample size and well-documented clinical traits, which increase the reliability of our findings. Three limitations of this study should be noted. First, this was a cross-sectional study, and thus we could not examine the cause-and-effect relationship between TIR and the development of DR. In addition, the cross-sectional measurement of TIR with 3-day CGM may not represent the historical glycemic control of the participants. Therefore the results of our study should be interpreted with caution. The fact that all patients were studied under the same dietary conditions mitigates some of these concerns. Nevertheless, our hypothesis-generating study can provide the basis for a prospective study with a similar design to clarify this issue. Second, the individuals enrolled in this study were hospital-based Chinese patients with type 2 diabetes. Therefore the results of our study might not be generalizable to all patients with diabetes from other ethnic groups. Third, CGM was conducted when patients adhered to a standard diet, which may not reflect the dietary patterns of participants in the real world. We could not determine whether these controlled dietary conditions resulted in an underestimation of the effect of TIR.

In conclusion, we provide evidence that TIR, as an intuitive metric of glycemic control for both patients and clinicians, is associated with the prevalence of DR in type 2 diabetes, and this association is independent of HbA_{1c}. Our findings suggest that TIR should be more broadly accepted as a research end point or clinical measure. Further prospective studies are warranted to obtain a definitive picture of the role of TIR in the onset and progression of DR.

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