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RESEARCH

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# Novel indicator of microvascular complications in patients with type 2 diabetes mellitus and shortened erythrocyte lifespan: a multicenter cross-sectional analysis

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## Abstract

**Introduction** In this study, we assessed whether the ratio of glucose management index (GMI) to glycated albumin (GA) was linked to microvascular complications in patients with type 2 diabetes mellitus (T2DM) who also possessed a shortened erythrocyte lifespan.

**Methods** This study encompassed individuals from the Tianjin Diabetic Retinopathy Screening Cohort who completed continuous glucose monitoring and had an erythrocyte lifespan of under 90 days. Differences in GMI/GA were compared between the T2DM patients with or without microvascular complications, including diabetic kidney disease (DKD) and diabetic retinopathy (DR). The relationship between GMI/GA and microvascular complications (DKD and/or DR) was assessed by dividing GMI/GA into three groups based on tertiles.

**Results** Our study comprised 140 participants with T2DM (62 men and 78 women, with a median age of 67 years) with a median DM duration of 9.68 years, a mean glycated hemoglobin A1c (HbA1c) value of 7.10%, and a median GA value of 16.10%. As expected, the lower GMI/GA group exhibited higher HbA1c and GA ($P < 0.001$) with similar mean glucose levels ($P = 0.099$). GMI/GA values were significantly higher in participants without microvascular complications than in those with microvascular complications, including DKD and/or DR ($P < 0.05$). After adjusting for confounders, the lowest GMI/GA group (T1) had a 3.601-fold increased risk of microvascular complications (95% *CI*, 1.364–9.508, $P = 0.010$) and a 3.830-fold increased risk of DKD, specifically (95% *CI*, 1.364–12.222, $P = 0.023$) relative to the highest group (T3).

**Conclusion** GMI/GA serves as a novel risk indicator for microvascular complications in T2DM, independent of HbA1c.

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**Keywords** Glycation rate, Glucose management index, Shortened erythrocyte lifespan, Continuous glucose monitoring, Microvascular complications, Type 2 diabetes mellitus

## Introduction

Diabetes mellitus (DM) is a leading cause of death and disability worldwide, without regard to age or sex of the individual; and it is projected that 1.31 billion people will be living with DM by 2050 [1]. Vascular complications that encompass the macrovascular and microvascular systems are significant contributors to morbidity and mortality in diabetic patients [2]. The pathogenesis of DM and its complications are complex, and primarily influenced by environmental and genetic factors [3]. Early studies have revealed variations in susceptibility to diabetic complications among patients with similar levels of diabetic glycemic control, clinical characteristics, and management [4].

Glycated hemoglobin A1c (HbA1c), reflecting blood glucose control over the previous three months, plays a key role in the diagnosis and management of DM. However, it has been observed that individuals with comparable glycemic control can exhibit significant variations in HbA1c values [5, 6]. Therefore, relying solely on HbA1c to establish a diagnosis of DM or to predict the risk of complications is not appropriate for all populations. Currently, many studies combine multiple biomarkers to improve the accuracy of disease prediction and assessment [7, 8]. In 2022 Maran et al. proposed a novel approach to assess glycosylation levels by calculating the ratio of the glycemic management index (GMI) to actual HbA1c, where GMI was the predicted HbA1c level based on average blood glucose values obtained by continuous glucose monitoring (CGM) [9]; and these authors demonstrated that in a type 1 diabetes mellitus (T1DM) population at similar glucose levels, patients with a rapid glycation phenotype (i.e., a GMI/HbA1c < 0.9) have an increased accumulation of advanced glycosylation end products (AGEs) in their skin that is strongly associated with the development of complications [10].

The level of HbA1c is primarily affected by three key factors: first, the HbA1c content in reticulocytes released from the bone marrow; second, the efficiency and level of glycosylation, where the level of glycosylation depends principally on blood glucose concentration, with individual variations in glycosylation efficiency; and third, the average lifespan of erythrocytes in the bloodstream, which determines the duration of hemoglobin (HB) exposure to glucose [11]. The normal erythrocyte lifespan is approximately 120 days, but in certain conditions such as iron-deficiency anemia, hemolytic anemia, and pregnancy, the erythrocyte lifespan can be shortened or lengthened, resulting in a mismatch between HbA1c and average blood glucose. In patients with type 2 diabetes mellitus (T2DM), the hyperglycemic environment and abnormal glycosylation can have adverse effects on hemoglobin and membrane proteins within erythrocytes. This not only leads to a decrease in erythrocyte membrane fluidity and a significant increase in erythrocyte osmotic fragility but also causes increased erythrocyte destruction [12, 13], ultimately resulting in anemia and a shortened erythrocyte lifespan. These conditions are fairly common and can impact the physician's clinical decision-making. Consequently, when blood glucose levels are similar but the erythrocyte lifespan is abnormal, a divergence occurs between actual HbA1c and predicted HbA1c results. HbA1c then becomes a less reliable index of glycemic control, requiring the exploration of new and more reliable indicators of glycemic control.

Glycated albumin (GA) is another glycated protein used clinically to assess glycemic status, unaffected by erythrocyte status [14]. In patients with a shortened erythrocyte lifespan, the GMI/GA ratio may provide an alternative to GMI/HbA1c for capturing individual differences in glycosylation. Therefore, the purpose of this study was to explore the relationship between GMI/GA and microvascular complications in T2DM patients with a shortened erythrocyte lifespan.

## Methods

### Study participants

This study was a multicenter cross-sectional observational study, approved by the Ethics Committee of Chu Hsien-I Memorial Hospital of Tianjin Medical University. Eligible patients were from the Tianjin Diabetic Retinopathy Screening Cohort. Inclusion criteria were: age ≥ 18 years; T2DM diagnosed according to the 2020 American Diabetes Association diagnostic criteria [15]; no history of smoking; CGM worn for at least 48 h; erythrocyte lifespan < 90 days; and complete clinical data. Additional exclusion criteria included a diagnosis of other types of DM; lack of specific data, including CGM data, erythrocyte longevity, or clinical data; presence of acute complications of DM; presence of concomitant diseases or treatments that affect glycemic control, such as acute infections or glucocorticoid therapy; and comorbidities that include acute or chronic hepatitis, cirrhosis, nephrotic syndrome, hyperthyroidism, or hypothyroidism that can affect albumin metabolism; or pregnant or lactating women. A flowchart of the participant screening process is depicted in Fig. 1.

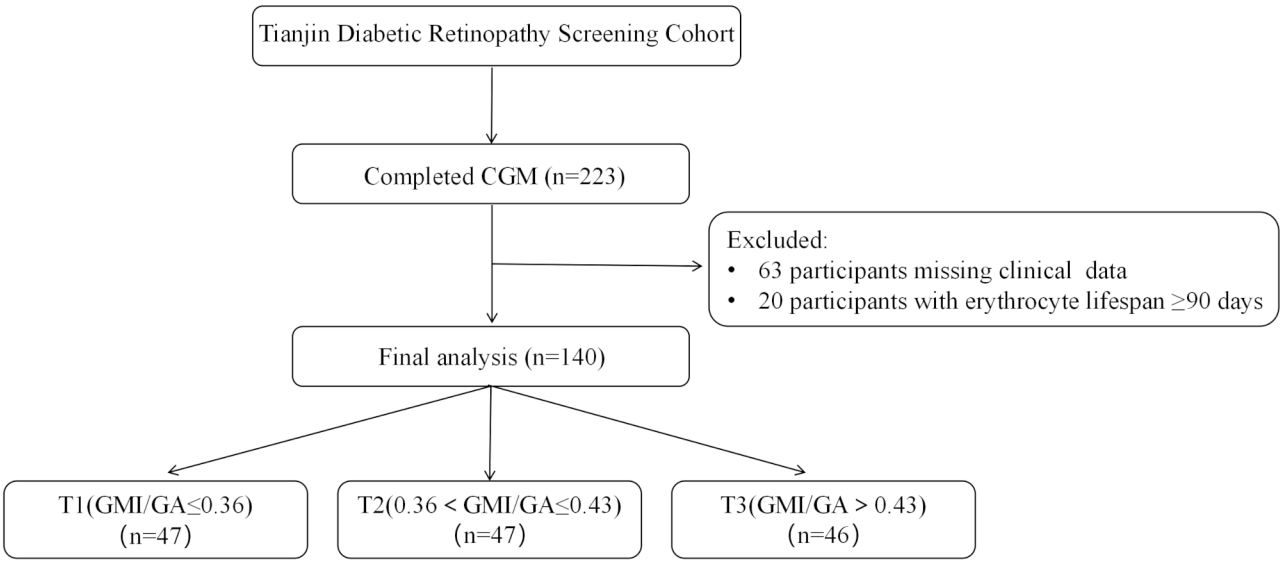



**Fig. 1** Flow chart of the study

### Covariates

We collected the age, sex, and duration of DM of each participant at enrollment. All participants underwent a physical examination to measure blood pressure (BP), height, and weight as previously described. We calculated body mass index (BMI) as weight (kg) divided by the square of the height ($m^2$).

All blood and urine samples were collected within one week of the CGM recording. Laboratory measurements included fasting plasma glucose (FPG), HbA1c, GA, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), serum creatinine (SCR), blood urea nitrogen (BUN), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), HB, and the urinary albumin-to-creatinine ratio (uACR). The estimated glomerular filtration rate (eGFR) was ascertained according to the CKD-EPI formula calculation [16].

### Continuous glucose monitoring

All participants wore a CGM device in the appropriate region following the manufacturer's instructions, and all CGM raw data were inspected by qualified study personnel. Data identified as invalid due to evidence of CGM malfunction or sensor loss were excluded from further analyses. Thus, only patients with >70% valid sensor data were included in the final analysis. There were no adjustments to the glucose-lowering regimen in the three months leading up to the use of the CGM device for blood glucose monitoring and during the period the patients wore the CGM.

### CGM Metrics

CGM metrics were determined under the latest international consensus on standards of CGM reporting [17]. Mean glucose (MG) was calculated as the average of all sensor glucose readings within the recording period; the GMI was calculated as 3.31 + 0.02393 × mean CGM glucose (mg/dL); and the coefficient of variation (CV) was estimated using the standard deviation (SD) of CGM glucose and MG (defined as SD/MG × 100%). We determined time in different glucose ranges according to the following definitions: time in range (TIR) (3.9–10 mmol/L), time in hypoglycemia (Low < 3.9 and VLow < 3.0 mmol/L), and time in hyperglycemia (High > 10 and VHigh > 13.9 mmol/L). The glycemic risk index (GRI) was calculated using the model built according to clinicians' rankings of CGM tracings by the original article, as GRI =(3.0 × VLow) + (2.4 × Low) + (1.6 × VHigh) + (0.8 × High) [18]. We also calculated TIR, time below range (TBR), and time above range (TAR), which were defined as the percent time spent in the range of 3.9–10 mmol/L, < 3.9 mmol/L and > 10 mmol/L, respectively.

### Erythrocyte lifespan test

We measured erythrocyte lifespan in conjunction with the carbon monoxide (CO) breath test, which is based on the rate of HB renewal. The principle is that hemoglobin produces CO during the degradation of HB in the body, and the lungs are the only channel for endogenous CO excretion. Approximately 86% of endogenous CO comes from hemoglobin degradation, and 85% of hemoglobin comes from the hemoglobin degradation process after erythrocyte destruction; therefore, approximately 70% of exhaled endogenous CO develops from erythrocyte

degradation. Thus, the CO excretion rate of the lungs can be extrapolated to the erythrocyte lifespan value, provided that exogenous interference is excluded [19]. Before sampling, the examinee took a deep breath, held it for 10 s, and then exhaled through the mouthpiece into the collection system. An ambient background air sample was collected using an air pump while the participant's alveolar gas was collected. We employed an ELS tester (Seekya Biotec Ltd., Shenzhen, China), which is an automated instrument for determining CO concentration by nondispersive infrared spectroscopy of paired alveolar and air gas samples. Erythrocyte lifespan was therefore calculated as: (d) = 1.38 × HB (g/L)/CO.

#### Outcomes and estimands

The primary outcome of interest was diabetic microvascular complications, including diabetic retinopathy (DR) and diabetic kidney disease (DKD). Microvascular complications were defined in this study as the presence of DR and/or DKD. DR was diagnosed by an ophthalmologist based on the results of digital retinal photography, and DKD was defined as the presence of microalbuminuria or macroalbuminuria (uACR ≥ 30 mg/g) or a diminution in eGFR to < 60 mL/min/1.73 $m^2$.

#### Statistical analysis

We evaluated data for normality and described them as mean and SD or median and interquartile range. Differences in baseline characteristics were investigated using one-way analysis of variance, Kruskal–Wallis test, or $\chi^2$ test for proportions, as appropriate. Post-hoc multiple comparison tests were performed using least-significant differences after one-way analysis. We performed a Bland–Altman analysis to evaluate the difference between GMI and HbA1c versus GMI. When GMI/GA was treated as a categorical variable, a logistic regression model was exploited to analyze the relationship between GMI/GA and the outcome (results were expressed as odds ratio [*OR*] and 95% confidence interval [95% *CI*]). Further subgroup analyses were performed, including sex (male and female), age (≤ 65 years and > 65 years), duration of DM (< 10 years and ≥ 10 years), BMI (≤ 26 kg/$m^2$ and > 26 kg/$m^2$), HbA1c (≤ 7% and > 7%), CV (< 30% and ≥ 30%), and TIR (< 85% and ≥ 85%).

We conducted analyses using SPSS version 27.0 software (SPSS Inc., Chicago, IL, USA) and Stata MP17, and plotted our data with GraphPad Prism 9.5. The reported statistical significance levels were all two-sided, with statistical significance set to 0.05.

## Results

#### Participant characteristics

We initially retrieved information on 223 individuals with T2DM who completed CGM. Of these, 63 were excluded because of missing clinical data, and 20 were excluded because their erythrocyte lifespan was ≥ 90 days. The characteristics of the 140 participants whom we ultimately included are presented in detail in Tables 1 and 2. Participants were divided into three groups based on the GMI/GA values using tertiles.

Of the 140 T2DM participants, 62 were men and 78 were women. Their median age was 67 years, the median duration of DM was 9.68 years, the median BMI was 26.38 kg/$m^2$, and the median systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 130 mmHg and 80 mmHg, respectively. There were no statistically significant differences in sex, age, duration of DM, BMI, or BP among the three groups ($P > 0.05$).

In terms of blood glucose control, the median FPG of individuals was 7.46 mmol/L, the average HbA1c was 7.10%, and the median GA was 16.10%. Although there was no difference in FPG among the three groups ($P > 0.05$), we noted significant differences in HbA1c and GA ($P < 0.05$); and the T3 group reflected the lowest value (mean HbA1c, 6.47%, and median GA, 13.16%), followed by the T2 group (mean HbA1c, 7.06%, and median GA, 16.10%), with the T1 group having the highest value (mean HbA1c, 7.77%, and median GA, 20.50%). The results of the CGM revealed that MG and GMI did not differ among the three groups ($P > 0.05$), with an overall median of 6.28 mmol/L and 6.89%, respectively. However, the other metrics that reflected glycemic variabilities such as CV, TIR, TAR, and GRI displayed significant differences across the groups ($P < 0.05$). In addition, except for slight differences in TG ($P < 0.05$), there were no differences in other lipid indices, liver and kidney function indices, HB, and uACR among the three groups ($P > 0.05$). The prevalence of microvascular complications was, however, significantly higher in patients in the T1 group than in those in the T3 group, as was the prevalence of DKD ($P > 0.05$).

We categorized participants into five groups based on the presence or absence of microvascular complications and the type of microvascular complications: no microvascular complications ($n = 67$, 47.86%), with DKD ($n = 40$, 28.57%), with DR ($n = 50$, 35.71%), with either DKD or DR ($n = 73$, 52.14%), and with both DKD and DR ($n = 17$, 12.14%). We observed that the GMI/GA ratio was higher in individuals with no microvascular complications relative to any of the other four groups (Fig. 2).

#### Bias between GMI and HbA1c

The Bland–Altman analysis (GMI minus HbA1c) displayed a negative bias of − 0.64% (95% limits of agreement, − 2.35–1.08%) overall. The limits of agreement were wider in participants with microvascular complications than in those without, and notably wider in those with DKD than in those with DR (Fig. 3).

**Table 1** Clinical characteristics of participants by GMI/GA tertiles

| Variable | T1(*n* = 47) | T2(*n* = 47) | T3(*n* = 46) | Total(*n* = 140) | *P*Value |
|---|---|---|---|---|---|
| **General condition** | | | | | |
| Sex(M/F) | 21/26 | 21/26 | 20/26 | 62/78 | 0.991 |
| Age(years) | 68(65,72) | 66(61,70) | 66(64,69) | 67(64,70) | 0.059 |
| Duration of DM(years) | 10.00(4.00,20.00) | 10.00(4.00,14.00) | 7.50(3.00,15.00) | 9.68(3.50,15.00) | 0.532 |
| SBP(mmHg) | 131.55(128.86,134.74) | 130.00(122.00,136.38) | 132.00(130.00,138.00) | 130.17(128.00,135.37) | 0.385 |
| DBP(mmHg) | 80.49(78.40,83.94) | 80.00(78.00,82.00) | 80.00(80.00,82.00) | 80.00(78.00,82.19) | 0.453 |
| BMI(kg/m$^2$) | 26.08(24.61,27.94) | 27.04(25.15,28.37) | 25.31(23.95,27.79) | 26.38(24.57,28.07) | 0.304 |
| **Clinical indicator** | | | | | |
| FPG(mmol/L) | 7.99(6.73,10.36) | 7.28(6.50,8.1) | 7.33(6.62,8.54) | 7.46(6.61,8.57) | 0.081 |
| HbA1C(%) | 7.77 ± 1.39***# | 7.06 ± 0.78** | 6.47 ± 0.72 | 7.10 ± 1.14 | <0.001 |
| GA(%) | 20.50(17.75,22.60)***#### | 16.10(15.58,17.20)*** | 13.16(12.60,14.60) | 16.10(14.32,18.11) | <0.001 |
| ALT(U/L) | 19.30(16.00,22.70) | 18.89(14.00,27.87) | 20.15(16.00,26.78) | 19.55(15.20,24.95) | 0.538 |
| AST(U/L) | 17.90(15.30,20.40) | 18.00(15.90,23.00) | 18.10(14.80,24.12) | 18.00(15.30,21.75) | 0.738 |
| TB(μmol/L) | 15.10(11.40,17.10) | 14.30(10.20,17.58) | 12.73(9.25,16.30) | 13.88(10.54,17.18) | 0.321 |
| SCR(μmol/L) | 63.00(50.50,79.70) | 58.40(55.55,74.93) | 56.69(51.00,72.80) | 58.80(53.00,74.33) | 0.478 |
| BUN(mmol/L) | 5.46(4.80,6.52) | 5.88(4.70,6.90) | 5.55(4.52,6.58) | 5.60(4.69,6.71) | 0.737 |
| eGFR(mL/min/1.73m$^2$) | 92.93(79.21,96.78) | 92.71(85.45,97.63) | 94.65(88.59,100.68) | 93.43(85.24,97.88) | 0.413 |
| TC(mmol/L) | 4.98 ± 1.20 | 5.24 ± 1.16 | 5.02 ± 1.00 | 5.08 ± 1.12 | 0.480 |
| TG(mmol/L) | 1.43(1.04,2.07) | 1.39(0.98,1.97) | 1.95(1.27,2.65) | 1.58(1.05,2.32) | 0.040 |
| LDL-C(mmol/L) | 2.81(2.17,3.41) | 3.00(2.42,3.75) | 3.12(2.20,3.61) | 3.03(2.25,3.69) | 0.740 |
| HDL-C(mmol/L) | 1.37(1.15,1.49) | 1.27(1.10,1.58) | 1.22(0.97,1.53) | 1.28(1.08,1.52) | 0.307 |
| HB(g/L) | 138.96 ± 14.69 | 135.34 ± 15.60 | 142.85 ± 17.03 | 139.02 ± 15.98 | 0.076 |
| Erythrocyte lifespan(d) | 65.00(56.69,74) | 67.00(56.00,73.00) | 61.53(54.28,71.00) | 65.00(55.00,72.00) | 0.504 |
| uACR(mg/g) | 22.50(4.60,49.00) | 8.99(5.60,19.40) | 12.40(4.10,25.30) | 11.48(5.05,30.01) | 0.209 |
| **Microvascular complications** | | | | | |
| DKD(*n*, %) | 20(42.55%)* | 12(25.53%) | 8(17.39%) | 40(28.57%) | 0.023 |
| DR(*n*, %) | 20(42.55%) | 18(38.30%) | 12(26.09%) | 50(35.71%) | 0.229 |
| DKD and/or DR(*n*, %) | 31(65.96%)* | 25(53.19%) | 17(36.96%) | 73(42.14%) | 0.020 |

* Compared with the T3 group, $P < 0.05$; ** compared with the T3 group, $P < 0.01$; *** compared with the T3 group, $P < 0.001$; # compared with the T2 group, $P < 0.05$; ## compared with the T2 group, $P < 0.01$; ### compared with the T2 group $P < 0.001$

**Table 2** CGM metrics of participants by GMI/GA tertiles

| Variable | T1(*n* = 47) | T2(*n* = 47) | T3(*n* = 46) | Total(*n* = 140) | *P*Value |
|---|---|---|---|---|---|
| Monitoring duration(d) | 13(9,15) | 14(7,15) | 13(8,15) | 13(8,15) | 0.790 |
| GMI(%) | 6.43(6.04,7.31) | 6.30(6.06,6.62) | 6.10(5.98,6.46) | 6.28(6.02,6.7) | 0.099 |
| MG(mmol/L) | 7.24(6.34,9.30) | 6.94(6.38,7.69) | 6.48(6.21,7.32) | 6.89(6.30,7.88) | 0.099 |
| CV(%) | 28.13 ± 5.97* | 28.66 ± 5.81* | 25.40 ± 5.59 | 27.41 ± 5.93 | 0.010 |
| TIR(%) | 84.50(67.62,90.81)* | 87.94(80.40,93.82) | 89.80(81.97,96.86) | 87.89(76.87,93.52) | 0.015 |
| TAR(%) | 21.53(3.78,32.37)* | 12.96(4.06,16.66) | 10.02(1.13,10.72) | 14.87(2.88,17.28) | 0.013 |
| TBR(%) | 2.88(0.08,4.71) | 2.80(0.58,3.88) | 3.78(0.62,4.22) | 3.14(0.42,4.09) | 0.878 |
| GRI(%) | 27.79(13.59,74.75)** | 16.33(8.74,44.47) | 12.23(5.47,24.47) | 18.70(9.39,49.48) | 0.003 |

* Compared with the T3 group, $P < 0.05$; ** compared with the T3 group, $P < 0.01$; *** compared with the T3 group, $P < 0.001$; # compared with the T2 group, $P < 0.05$; ## compared with the T2 group, $P < 0.01$; ### compared with the T2 group $P < 0.001$

### Microvascular complications associated with the GMI/GA

Without adjusting for any variables, the T1 group exhibited a 3.305-fold higher risk of microvascular complications (*OR*, 3.305; 95% *CI*, 1.413–7.733; $P = 0.006$) and a 3.519-fold increased risk of DKD (*OR*, 3.519; 95% *CI*, 1.351–9.161; $P = 0.010$) compared to the T3 group. The association between GMI/GA and microvascular complications (i.e., either DKD or DR or both) remained statistically significant after adjusting for age, sex, DM duration, BMI, ALT, AST, SCR, BUN, TC, TG, LDL, and HB. Compared to participants in the T3 group, those in the T1 group had an *OR* (95% *CI*) of 3.601 (1.364–9.508) for microvascular complications and 3.830 (1.200–12.222) for DKD. However, we never observed a statistically significant relationship between GMI/GA and DR in our study, with or without adjusting for variables (Table 3).

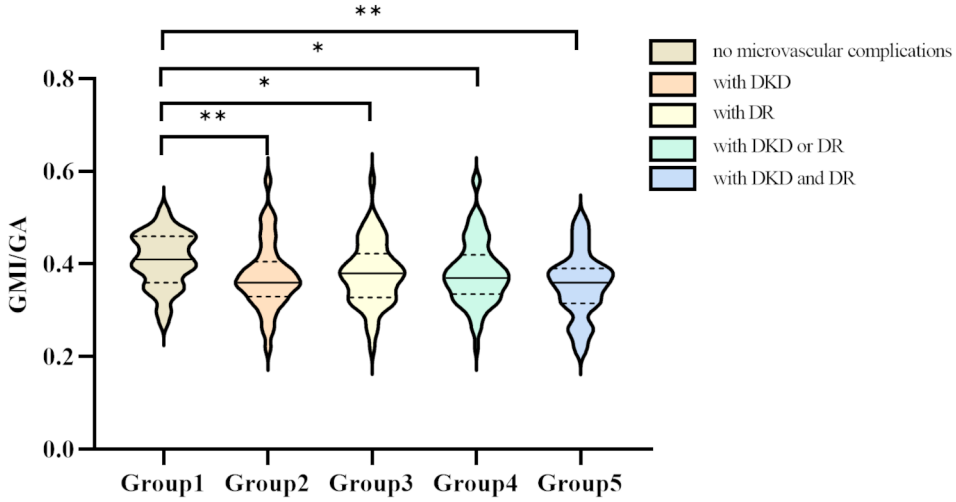



**Fig. 2** Violin plots of GMI/GA comparisons in different populations
Group1: no microvascular complications; Group2: with DKD; Group3: with DR; Group4: with either DKD or DR; Group5: with both DKD and DR
*$P < 0.05$; **$P < 0.01$

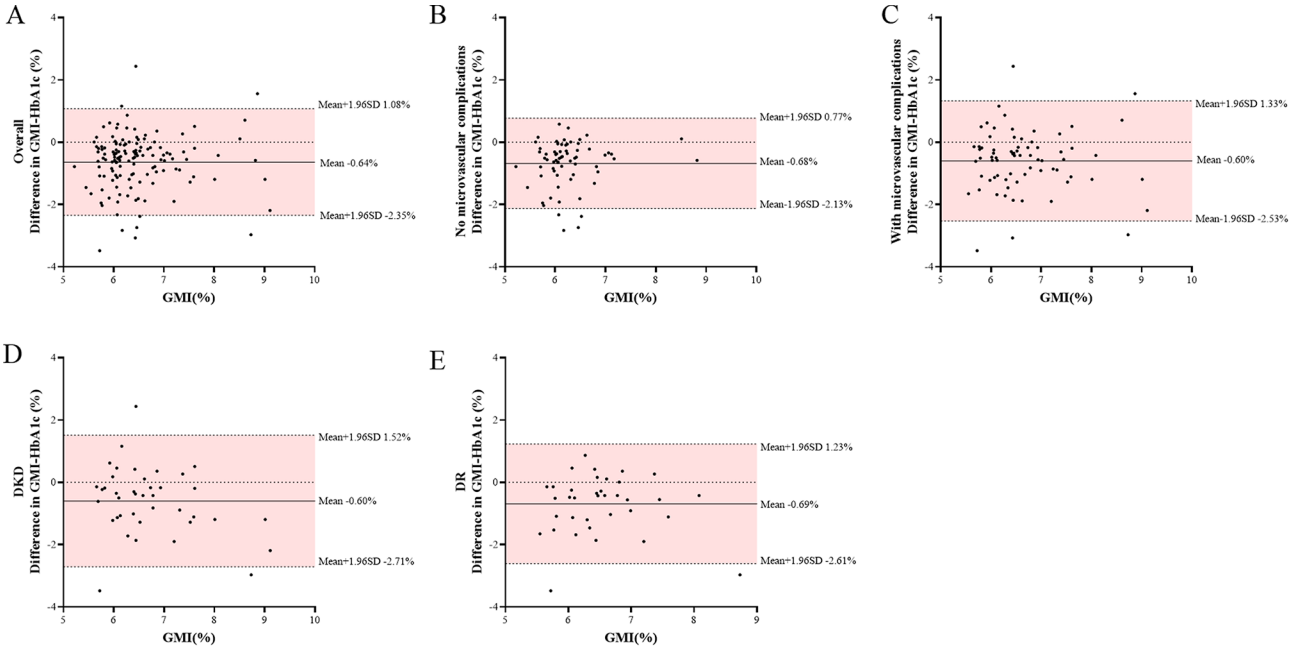



**Fig. 3** Bland–Altman plot for difference between GMI and HbA1c
**A**: overall; **B**: no microvascular complications; **C**: with either DKD or DR; **D**: with DKD; **E**: with DR

### Subgroup analyses for the associations between GMI/GA and microvascular complications

Subgroup analysis revealed that the incidence of microvascular complications and DKD was significantly higher in the T1 group relative to the T3 group in women, those aged ≤ 65 years, individuals with DM ≥ 10 years, a BMI > 26 kg/m$^2$, and a CV < 30% (all $P < 0.05$). The prevalence of microvascular complications was statistically higher in the T1 and T2 groups among individuals with a TIR < 85% (all $P < 0.05$). Furthermore, the prevalence of microvascular complications was significantly higher in the T1 and T2 groups than in the T3 group in the population with HbA1c > 7% (all $P < 0.05$). We noted no associations in the remaining subgroups (all $P > 0.05$), and there were no interactions between the GMI/GA and any variables (Figs. 4 and 5).

## Discussion

This cross-sectional study was the first-ever to depict a correlation between GMI/GA and microvascular complications in T2DM patients with shortened erythrocyte lifespan. Elevated GMI/GA appeared to reduce the risk

**Table 3** ORs (95% *CIs*) of microvascular complications according to the GMI/GA of individuals with T2DM

| | | Microvascular complications(DKD and/or DR) | | | DKD | | | DR | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **OR** | **95%CI** | ***P*Value** | **OR** | **95%CI** | ***P*Value** | **OR** | **95%CI** | ***P*Value** |
| Model 1 | T1 | 3.305 | 1.413–7.733 | 0.006 | 3.519 | 1.351–9.161 | 0.010 | 2.099 | 0.874–5.040 | 0.097 |
| | T2 | 1.939 | 0.846–4.440 | 0.117 | 1.629 | 0.596–4.452 | 0.342 | 1.759 | 0.728–4.251 | 0.210 |
| | T3 | Ref | | | Ref | | | Ref | | |
| Model 2 | T1 | 3.653 | 1.463–9.119 | 0.006 | 3.651 | 1.349–9.881 | 0.011 | 2.271 | 0.881–5.852 | 0.089 |
| | T2 | 2.202 | 0.902–5.374 | 0.083 | 1.752 | 0.625–4.909 | 0.286 | 1.952 | 0.759–5.02 | 0.165 |
| | T3 | Ref | | | Ref | | | Ref | | |
| Model 3 | T1 | 3.601 | 1.364–9.508 | 0.010 | 3.830 | 1.200-12.222 | 0.023 | 1.957 | 0.728–5.259 | 0.183 |
| | T2 | 1.749 | 0.659–4.645 | 0.262 | 1.076 | 0.309–3.746 | 0.909 | 1.607 | 0.574–4.495 | 0.366 |
| | T3 | Ref | | | Ref | | | Ref | | |

Model 1: unadjusted for variables

Model 2: adjusted for age, sex, DM duration and BMI

Model 3: adjusted for ALT, AST, SCR, BUN, TC, TG, LDL, and HB based on model 2

*OR*: odds ratio; 95%*CI*: 95% confidence level

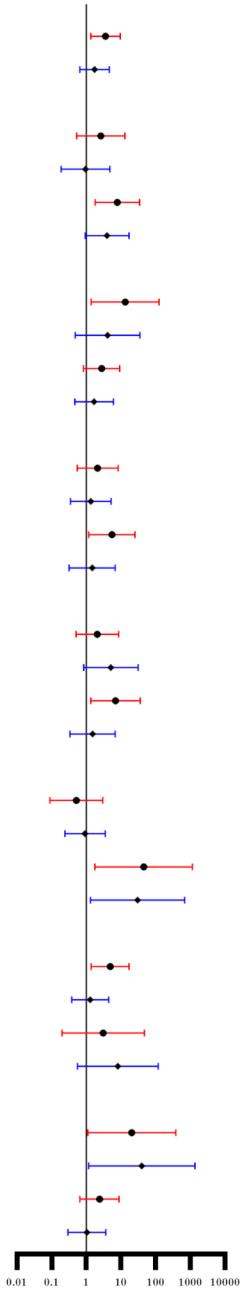
of microvascular complications in patients with T2DM, particularly with respect to the occurrence of DKD.

HbA1c serves as a crucial indicator of long-term blood glucose control and generally correlates well with blood glucose concentrations [20]. It has been also established that HbA1c is linked to the risk of developing microvascular complications in DM. However, a variety of factors that affect erythrocyte survival or regulate intracellular glucose concentrations can influence HbA1c independently of blood glucose levels [11, 21]. The authors of the ACCORD study ascertained that—compared to standard treatment—intensive treatment aimed at achieving normal HbA1c levels for 3.5 years not only failed to reduce the occurrence of major cardiovascular events but also increased mortality [22]. Sheng et al. further analyzed the ACCORD study and found that HbA1c variability was a strong predictor of all-cause mortality [23]. Any factor that significantly alters glycosylation would theoretically disrupt the relationship between glucose and the development of diabetic complications, including the glycation rate. We herein discerned that T2DM participants presenting with microvascular complications (either DKD or DR or both) possessed significantly lower GMI/GA values than those without microvascular complications. Further analysis revealed a significant correlation between GMI/GA and the development of microvascular complications in T2DM, partly reflecting the relationship between an individual's glycosylation rate and microvascular complications in T2DM. HbA1c may deviate from blood glucose values due to inter-individual differences in intra-erythrocyte glycation, leading to a lower (lower hemoglobin glycation index [HGI] connotes a lower rate of glycation) or higher (higher HGI reflects a higher rate of glycation) than expected HbA1c [24]. Our results showed a wider range of agreement for the bias between GMI and HbA1c in participants with microvascular complications than in those without microvascular complications, partially explaining the possibility of higher glycation rates in participants with microvascular complications.

Diabetic microangiopathy (encompassing DKD and DR) is a consequence of prolonged suboptimal glycemic control in patients with DM, and the levels of AGEs determined in serum were shown to be closely related to blood glucose control in patients with T2DM [25]. Hyperglycemia exacerbates protein glycation and precipitates progressive accumulation of AGEs in tissues, reflecting a significant role in the pathogenesis of diabetic complications [26, 27]. Investigators have previously observed in patients with T1DM that the lower the GMI/HbA1c, the higher the accumulation of skin AGEs and the higher the incidence of microvascular complications [10]. The relationship between AGEs and microvascular complications has also been confirmed by several clinical studies [28–30]. In the present study, both GMI and GA reflected patients' glycemic control over the same period, and there was a moderate positive correlation between them. We used the ratio of theoretical protein glycation level (GMI) to actual protein glycation level (GA) to indirectly demonstrate the differences in individual glycation rates. The faster the glycation rate at the same blood glucose level, the higher the accumulation of AGEs in the tissues and the higher the incidence of microvascular complications, which is consistent with the results of previous studies. However, there were some limitations to the present study, as it was a cross-sectional study in which we could not determine any causal relationship between GMI/GA and the occurrence of microvascular complications; this would require validation through large-scale prospective cohort studies.

The role of AGEs in the development of diabetic complications is relatively well defined [31], as they can harm blood vessels and tissues, either by direct accumulation or by binding to their receptor advanced glycosylation

| Subgroup | Number of participants | Case(%) | *OR* (95%*CI*) | $P_{interaction}$ |
|---|---|---|---|---|
| **Total** | 140 | 73(42.14%) | 3.601(1.364-9.508) | |
| | | | 1.749(0.659-4.645) | |
| **Sex** | | | | 0.320 |
| Male | 62 | 35(56.45%) | 2.615(0.528-12.943) | |
| | | | 0.957(0.190-4.814) | |
| Female | 78 | 38(48.72%) | 7.909(1.817-34.428) | |
| | | | 3.990(0.936-17.014) | |
| **Age(years)** | | | | 0.677 |
| ≤65 | 53 | 25(47.17%) | 13.199(1.384-125.862) | |
| | | | 4.086(0.478-34.944) | |
| >65 | 87 | 48(55.17%) | 2.766(0.835-9.156) | |
| | | | 1.683(0.470-6.021) | |
| **Duration of DM(years)** | | | | 0.355 |
| <10 | 70 | 29(41.43%) | 2.133(0.548-8.303) | |
| | | | 1.357(0.352-5.234) | |
| ≥10 | 70 | 44(62.86%) | 5.480(1.191-25.206) | |
| | | | 1.480(0.320-6.841) | |
| **BMI(kg/m$^2$)** | | | | 0.290 |
| ≤26 | 65 | 37(56.92%) | 2.088(0.507-8.597) | |
| | | | 5.144(0.848-31.205) | |
| >26 | 75 | 36(48.00%) | 6.933(1.344-35.747) | |
| | | | 1.527(0.339-6.868) | |
| **HbA1C(%)** | | | | 0.153 |
| ≤7 | 77 | 33(42.86%) | 0.520(0.089-3.033) | |
| | | | 0.924(0.241-3.538) | |
| >7 | 63 | 40(63.49%) | 45.070(1.779-1141.932) | |
| | | | 30.176(1.327-686.431) | |
| **CV(%)** | | | | 0.643 |
| <30 | 93 | 44(47.31%) | 4.867(1.382-17.138) | |
| | | | 1.304(0.383-4.438) | |
| ≥30 | 47 | 29(61.70%) | 3.059(0.199-46.974) | |
| | | | 8.14(0.558-118.723) | |
| **TIR(%)** | | | | 0.524 |
| <85 | 54 | 37(68.52%) | 20.535(1.109-380.248) | |
| | | | 39.809(1.176-1348.059) | |
| ≥85 | 86 | 36(41.86%) | 2.407(0.656-8.834) | |
| | | | 1.041(0.297-3.651) | |



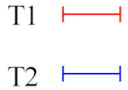




**Fig. 4** Subgroup analyses of the association between the GMI/GA and microvascular complications (DKD and/or DR)
Adjusted for age, sex, DM duration, BMI, ALT, AST, SCR, BUN, TC, TG, LDL, and HB. The strata variable was not included in our model when stratifying by itself. Red represents an increased risk of microvascular complications in the T1 group compared with the T3 group, and blue represents an increased risk of microvascular complications in the T2 group compared with the T3 group

end products (RAGEs), triggering downstream signaling pathways. Elevated AGEs have been uncovered in both retina [32] and glomeruli [33] in the context of DM. The potential importance of AGEs in the pathogenesis of diabetic complications was also revealed by the observation that two structurally different inhibitors of AGEs partially ameliorated diabetic microvascular disease in the retina and kidney in animal models [34, 35]. The production of intracellular AGE precursors damages target cells through three main mechanisms: first, the function of intracellular proteins modified by AGEs is compromised; second, extracellular matrix components modified by AGE precursors interact abnormally with other matrix components and matrix protein (integrin) receptors on

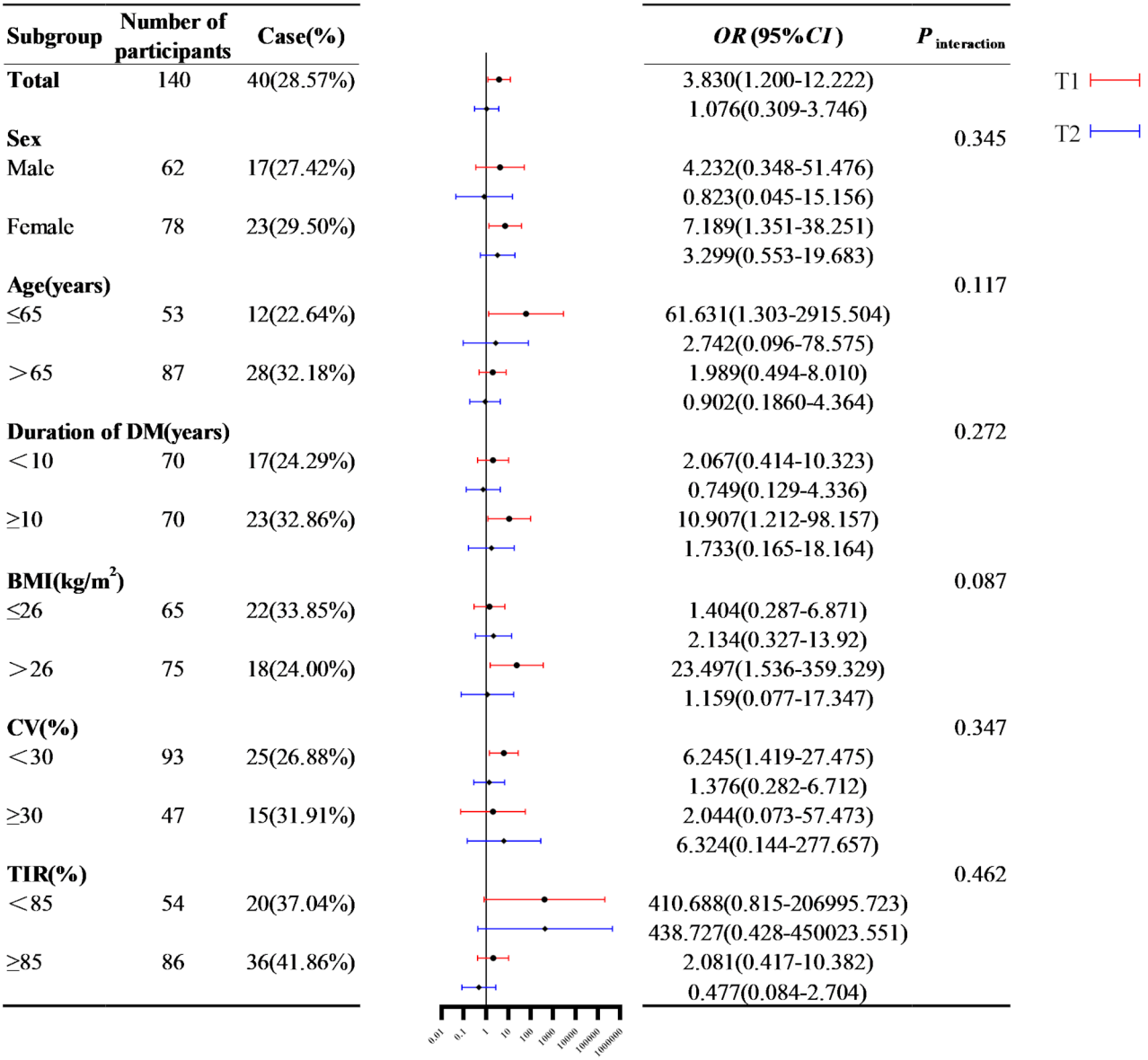



**Fig. 5** Subgroup analyses of the association between the GMI/GA and DKD
Adjusted for age, sex, DM duration, BMI, ALT, AST, SCR, BUN, TC, TG, LDL, and HB. The strata variable was not included in our model when stratifying by itself. Red represents an increased risk of microvascular complications in the T1 group compared with the T3 group, and blue represents an increased risk of microvascular complications in the T2 group compared with the T3 group

the cells; and third, plasma proteins modified by AGE precursors bind to the RAGEs on endothelial cells, tethered membrane cells, and macrophages—inducing generation of receptor-mediated reactive oxygen species [36]. This indicator holds promise as an effective tool for screening individuals who may benefit from treatments aimed at inhibiting AGE production to the progression of T2DM microvascular complications. The GMI/GA ratio can also be used to indirectly indicate the generation of AGEs in T2DM, and this index might serve as a reference for screening individuals who could benefit from treatments aimed at inhibiting AGE generation to decelerate the progression of microvascular complications in T2DM. These therapeutic measures encompass increasing the intake of anti-glycation foods; engaging in regular physical activity; and employing antioxidant medications and other interventions to directly or indirectly intervene in the glycation process.

Our study revealed that a lower GMI/GA ratio was strongly associated with the development of microvascular complications, particularly with an increased risk for DKD; while the correlation with DR was not significant. The discordance between DKD and DR (DKD-positivity and DR-negativity, or DKD-negativity and DR-positivity)

in patients with T2DM is not a novel finding. The authors of a study involving five cities in China demonstrated a discordance between DR and DKD of 39.7% in patients with T2DM [37], and a multicenter study in Italy depicted a discordance of 36.6% between DKD and DR [38]. In the present study, the discordance reached 52.14%. Although there was a possible inconsistency between DKD and DR due to the small sample size, the fact that DKD and DR were discordant cannot be ignored. DKD and DR share similar underlying mechanisms, but numerous investigators postulate that DKD and DR may still differ in certain aspects. Authors of a Swedish study clustered patients with newly diagnosed DM based on six variables (glutamate decarboxylase antibodies, age at diagnosis, BMI, HbA1c, homoeostatic model assessment, and two estimates of β-cell function and insulin resistance), and ascertained that the risk of DKD was higher in the cluster with the most resistance to insulin, and that the risk of DR was highest in the cluster with insulin deficiency [39]. Additionally, the novel hypoglycemic agents, sodium-glucose co-transporter protein 2 inhibitors and glucagon-like peptide receptor agonists, displayed prominent renoprotective effects, but not retinoprotective effects [40]. All of this evidence indirectly reflected differences in pathogenesis between DKD and DR. Therefore, it is necessary to continue to expand the sample size so as to verify the relationship between GMI/GA and microvascular complications associated with T2DM.

Our study was an initial effort to assess the predictive value of GMI/GA on the risk of microvascular complications in patients with T2DM who also possess shortened erythrocyte lifespan. The underlying mechanisms are not fully understood, and more prospective studies are needed to further explore this risk prediction. Nevertheless, our research retains substantial clinical value. First, the GMI/GA ratio may assist clinicians in identifying patients at high risk for DKD and DR, enabling early intervention and prevention. Second, this ratio could serve as an indicator for indirectly reflecting the generation of AGEs in T2DM patients, offering a new perspective for assessing the risk of complications. Third, the GMI/GA ratio might become a powerful tool for screening individuals who could benefit from AGE inhibitor therapy, thereby helping to slow the progression of T2DM microvascular complications and providing support for developing personalized treatment strategies. Additionally, our research highlights the importance of considering that in individuals with a shorter erythrocyte lifespan, HbA1c may not accurately reflect actual blood glucose levels. Therefore, in clinical practice, it is crucial to combine other indicators to comprehensively assess patients' true glycemic status, avoiding the oversight of potential risks due to seemingly normal HbA1c levels.

The present study exhibits notable advantages. First, our study is a multicenter study with participants from multiple communities. Second, the population included in this study was sourced from the community with a more stable glucose-lowering regimen, eliminating the inconsistency between CGM results and measured GA and HbA1c levels; such inconsistency is often caused by fluctuations in blood glucose due to changes in the glucose-lowering regimen. Third, we obtained blood glucose levels from CGM that were more accurate than estimating HbA1c from fasting glucose or self-glucose monitoring. Fourth, we quantified erythrocyte lifespan with the CO breath test. Fifth, we excluded the interference of smoking on microangiopathy. Finally, the study focuses on a novel composite indicator, exploring its potential in predicting diabetic microvascular complications and improving the accuracy of disease prediction and assessment. The sample size of our study was also relatively small, and bias could not be completely eliminated despite adjusting for confounders in the data analysis.

## Conclusions

Our study revealed that in a T2DM population with a shortened erythrocyte lifespan, patients with lower GMI/GA may experience a more rapid rate of glycosylation, which in turn increases their susceptibility to microvascular complications. We thereby posit that the GMI/GA is a novel risk indicator of T2DM microvascular complications, independent of HbA1c.

**Abbreviations**

| | |
|---|---|
| DM | Diabetes mellitus |
| HbA1c | Glycated hemoglobin A1c |
| GMI | Glucose management index |
| CGM | Continuous glucose monitoring |
| T1DM | Type 1 diabetes mellitus |
| AGEs | Advanced glycosylation end products |
| HB | Hemoglobin |
| T2DM | Type 2 diabetes mellitus |
| GA | Glycated albumin |
| BP | Blood pressure |
| BMI | Body mass index |
| FPG | Fasting plasma glucose |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| TB | Total bilirubin |
| SCR | Serum creatinine |
| BUN | Blood urea nitrogen |
| TC | Total cholesterol |
| TG | Triglyceride |
| LDL-C | Low-density lipoprotein cholesterol |
| HDL-C | High-density lipoprotein cholesterol |
| uACR | Urinary albumin-to-creatinine ratio |
| eGFR | Estimated glomerular filtration rate |
| MG | Mean glucose |
| CV | Coefficient of variation |
| SD | Standard deviation |
| TIR | Time in range |
| GRI | Glycemic risk index |
| TBR | Time below range |
| TAR | Time above range |
| CO | Carbon monoxide |

| | |
|---|---|
| DR | Diabetic retinopathy |
| DKD | Diabetic kidney disease |
| OR | Odds ratio |
| CI | Confidence interval |
| SBP | Systolic blood pressure |
| DBP | Diastolic blood pressure |
| HGI | Hemoglobin glycation index |
| RAGEs | Receptor advanced glycosylation end products |

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**Author contributions**
YQW, PY, SJZ and XLW were responsible for the conceptualization of the study; YQW and BSZ analyzed the statistics; BSZ and XM collected data; YQW prepared figures and tables; YQW wrote the original manuscript; PY, SJZ and XLW reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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**Data availability**
Restrictions apply to the availability of data generated or analyzed during this study because they were used under license to preserve patient confidentiality. Data are, however, available from the authors upon reasonable request.

## Declarations

**Ethics approval and consent to participate**
This study was approved by the Ethics Committee of Chu Hsien-I Memorial Hospital of Tianjin Medical University.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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