Negative association of time in range and urinary albumin excretion rate in patients with type 2 diabetes mellitus: a retrospective study of inpatients

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Abstract

Background: Time in range (TIR) refers to the time an individual spends within their target glucose range, which now has been popularized as an important metric to classify glycemic management and also recognized as an important outcome of current diabetes therapies. This study aimed to investigate the association between TIR and the severity of the urinary albumin excretion rate (UAER) in patients with type 2 diabetes mellitus (T2DM).

Methods: We retrospectively analyzed the data of 1014 inpatients with T2DM at the Department of Endocrinology and Metabolism of Peking University International Hospital, China. TIR was defined as the percentage of blood glucose within the target range of 3.90–10.00 mmol/L. Urine samples for assessment of UAER were collected for 3 consecutive days from the start of hospitalization.

Results: The TIR values for patients with normal urine levels of albumin, microalbuminuria, and macroalbuminuria were 70% ± 20%, 50% ± 20%, and 30% ± 20%, respectively (all P < 0.001). The patients were stratified according to quartiles of TIR as follows: quartile (Q) 1, <55%; Q2, 55%–72%; Q3, 73%–83%; and Q4, >83%. The incidences of microalbuminuria in Q1, Q2, Q3, and Q4 were 41.1%, 21.6%, 7.1%, and 5.5% (all P < 0.001), respectively. The respective incidences of macroalbuminuria were 24.2%, 1.1%, 1.4%, and 0% (all P < 0.001). In multinomial logistic regression analyses, TIR was significantly correlated with microalbuminuria (odds ratio [OR] 0.58, 95% confidence interval [CI]: 0.32–0.65, P < 0.001) and macroalbuminuria (OR 0.26, 95% CI: 0.18–0.38, P < 0.001) after adjusting for age, sex, body mass index, diabetes duration, systolic blood pressure, and levels of triglycerides, glycosylated hemoglobin A1c, and creatinine.

Conclusion: The proportion of blood glucose in TIR is closely related to the severity of UAER in patients with T2DM.

Keywords: Time in range; Type 2 diabetes; Urinary albumin excretion rate; Blood glucose frequency and duration of hypoglycemia or hyperglycemia improve over time. It has become an important metric for classifying glycemic management and is recognized as an important outcome of current therapies for diabetes.[4,5]

Diabetic nephropathy, more commonly known as diabetic kidney disease, remains a major cause of morbidity and mortality in T2DM patients. It is clinically defined by the presence of impaired renal function and/or elevated urinary albumin excretion rate (UAER) and is the main cause of end-stage renal disease in both developed and developing countries.[6-8] Microalbuminuria is the early clinical manifestation of diabetic nephropathy and is the main basis for its diagnosis. Despite the use of TIR for assessing glycemic control, the relationship between TIR and UAER in patients with T2DM remains unknown. Therefore, we investigated the association between TIR...
measured from fingerstick samples and the severity of UAER in patients with T2DM.

Methods

Ethics approval

The study was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Peking University International Hospital (No. 2021-044[biomedical research]).

Participants

We retrospectively analyzed the data of 1014 inpatients with T2DM at the Department of Endocrinology and Metabolism of Peking University International Hospital from January 2018 to December 2019. T2DM was diagnosed according to the 1999 World Health Organization criteria. Inclusion criteria were age ≥18 years, presence of T2DM, and a stable glucose-lowering regimen over the previous 3 months. Exclusion criteria included diabetic ketoacidosis, hyperglycemic hyperosmolar state, severe and recurrent hypoglycemic events within the preceding 1 month, patients with incomplete data, and a history of malignancy, mental disorders, heart failure, or severe kidney or liver dysfunction.

Biochemical and physiological parameters

Patient baseline data were obtained from the Electronic Medical Record System of our hospital, and included age, gender, height, body weight, blood pressure, duration of T2DM, estimated glomerular filtration rate (eGFR), and levels of HbA1c, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and creatinine.

Glycemic metrics

Blood levels of glucose measured from fingerstick samples were taken 6 times a day (at 0 a.m., at 3 a.m., after waking up and after fasting, and after each of 3 meals) from all patients for 3 consecutive days. TIR was defined as the percentage of blood glucose within the target range of 3.90–10.00 mmol/L during a 24-hour period. After the 3-day monitoring period, TIR was calculated. The glucose coefficient of variation was calculated by dividing the standard deviation (SD) of each glucose reading by its corresponding mean. The mean amplitude of glycemic excursions was calculated by measuring the arithmetic mean of the differences between consecutive peaks and nadirs, and only excursions of >1 SD of the mean glycemic value were considered.

Assessment of UAER

All participants were instructed to begin collecting urine after discarding the first morning urine until the collection of first voided urine sample next morning in a provided receptacle. Urine samples for assessment of UAER were collected for 3 consecutive days from the start of hospitalization. UAER was detected via immunoturbidimetry. Creatinine levels were determined using an enzymatic method. The severity of UAER was classified as normal (urine levels of albumin <30 mg/g), microalbuminuria (levels of 30–300 mg/g), and macroalbuminuria (levels >300 mg/g).

Statistical analyses

The sample size of the study was based on the study period and the inclusion criteria with a two-sided alpha value of 0.05. As approximately a total of 10 confounders were expected to adjust in the multivariable Logistic regression model, a minimal of 100 events (i.e., primary outcomes macroalbuminuria) were needed. Since there were overall 182 patients developed macroalbuminuria, the sample size was considered enough for this analysis. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc, North Carolina, United States). Continuous variables were assessed using linear polynomial contrasts in analysis of variance for normally distributed variables and the Jonckheere–Terpstra test for non-normally distributed data. Univariate multinomial logistic regression was conducted to assess the associations between TIR and the severity of UAER. Additional multivariate multinomial logistic regression analyses were performed. In addition, univariate and multivariate binary logistic regressions were used to evaluate the associations between TIR and UAER. Delete method was used to deal with missing values. A P value < 0.05 was considered statistically significant.

Results

Baseline characteristics

The characteristics of the 1014 patients examined in the current study are presented in Table 1. The mean age was 55.6 years, diabetes duration was 8.9 years, body mass index (BMI) was 26.00 kg/m², and HbA1c was 8.40%.

Percentage of TIR and the severity of UAER

Across all patients, the percentage of TIR was 70% ± 20%. Those for the normal, microalbuminuria, and macroalbuminuria groups were 70% ± 20%, 50% ± 20%, and 30% ± 20%, respectively (all P < 0.001). The severity of UAER was inversely correlated with TIR percentage. Next, the patients were stratified according to quartiles of TIR, as follows: quartile (Q) 1, <55% (n = 231); Q2, 55%–72% (n = 264); Q3, 73%–83% (n = 211); and Q4, >83% (n = 308). The prevalences of microalbuminuria in Q1, Q2, Q3, and Q4 were 41.1% (95/231), 21.6% (57/264), 7.1% (15/211), and 5.5% (17/308), respectively (all P < 0.001). The respective prevalences of macroalbuminuria were 24.2% (56/231), 1.1% (3/264), 1.4% (3/211), and 0% (0/308) (all P < 0.001).

Multinomial logistic regression of the severity of UAER and TIR

Univariate analyses indicated that TIR was significantly associated with microalbuminuria (odds ratio [OR] 0.56, 95% confidence interval [CI]: 0.51–0.62, P < 0.001) and macroalbuminuria (OR 0.36, 95% CI: 0.29–0.44,
Table 1: Baseline characteristics of patients with T2DM by the severity of UAER.

| Variables                        | All subjects (n = 1014) | Normal (n = 768) | Microalbuminuria (n = 184) | Macroalbuminuria (n = 62) | Z/F/χ² statistics | P value |
|----------------------------------|-------------------------|------------------|---------------------------|--------------------------|--------------------|---------|
| Male/female                      | 637/377                 | 485/283         | 115/69                    | 37/25                    | -0.505             | 0.614   |
| Age (years)                      | 55.6 ± 13.9             | 54.4 ± 13.6     | 58.5 ± 14.9               | 61.3 ± 12.0              | 14.43              | < 0.001 |
| Diabetes duration (years)        | 8.9 ± 7.7               | 7.9 ± 7.2       | 10.9 ± 8.2                | 15.2 ± 8.4               | 35.22              | < 0.001 |
| BMI (kg/m²)                      | 26.00 ± 3.70            | 26.00 ± 3.70    | 26.30 ± 3.80              | 25.60 ± 4.10             | 0.44               | 0.507   |
| SBP (mmHg)                       | 132.0 ± 15.8            | 130.5 ± 15.4    | 135.0 ± 16.1              | 141.5 ± 15.5             | 28.78              | < 0.001 |
| DBP (mmHg)                       | 77.2 ± 10.0             | 76.9 ± 10.2     | 77.5 ± 9.1                | 79.0 ± 9.6               | 2.58               | 0.109   |
| Creatinine (mmol/L)              | 70.00 ± 21.90           | 67.10 ± 15.50   | 73.70 ± 27.20             | 94.40 ± 44.30            | 98.08              | < 0.001 |
| eGFR (mL/min⁻¹·1.73 m⁻²)         | 96.50 ± 19.90           | 99.30 ± 16.80   | 92.20 ± 23.40             | 75.90 ± 27.80            | 87.20              | < 0.001 |
| HbA1c (%)                        | 8.40 ± 2.00             | 8.20 ± 1.90     | 9.20 ± 2.20               | 9.60 ± 2.10              | 29.91              | < 0.001 |
| Fasting C-peptide (ng/mL)        | 2.50 ± 1.70             | 2.50 ± 1.60     | 2.60 ± 1.50               | 3.00 ± 3.00              | 6.03               | 0.014   |
| CV (%)                           | 30.00 ± 10.00           | 30.00 ± 10.00   | 30.00 ± 10.00             | 30.00 ± 10.00            | 11.11              | 0.001   |
| MAGE                              | 4.60 ± 2.00             | 4.30 ± 1.80     | 5.40 ± 2.10               | 6.70 ± 2.40              | 87.96              | < 0.001 |
| Total cholesterol (mmol/L)       | 4.30 ± 1.10             | 4.30 ± 1.10     | 4.30 ± 1.30               | 5.00 ± 1.50              | 21.65              | < 0.001 |
| Triglyceride (mmol/L)            | 2.00 ± 1.70             | 2.00 ± 1.70     | 2.10 ± 1.50               | 2.40 ± 1.80              | 4.76               | 0.029   |
| HDL-C (mmol/L)                   | 1.00 ± 0.30             | 1.00 ± 0.30     | 1.00 ± 0.30               | 1.10 ± 0.40              | 5.24               | 0.022   |
| LDL-C (mmol/L)                   | 2.50 ± 0.90             | 2.50 ± 0.90     | 2.50 ± 1.00               | 2.80 ± 1.10              | 5.03               | 0.025   |
| Hypoglycemic regimen             |                         |                 |                           |                          |                    |         |
| Oral antidiabetes drugs          | 1004 (99)               | 768 (100)       | 178 (97)                  | 62 (100)                 | –                  | < 0.001 |
| Insulin                          | 497 (49)                | 261 (34)        | 120 (65)                  | 30 (48)                  | 61.76              | < 0.001 |

Deppressurization scheme

| Parameters                        | Microalbuminuria | Macroalbuminuria | Albuminuria |
|-----------------------------------|------------------|------------------|-------------|
| Univariable analysis              |                  |                  |             |
| TIR                               | 0.56 (0.51, 0.62)| 0.36 (0.29, 0.44)| 0.36 (0.29, 0.44)| 0.52 (0.47, 0.57)| 109.21|< 0.001|
| Multivariable analysis            |                  |                  |             |
| TIR, Model 1                      | 0.58 (0.52, 0.65)| 0.26 (0.18, 0.38)| 0.26 (0.18, 0.38)| 0.54 (0.48, 0.60)| 127.99|< 0.001|
| TIR, Model 2                      | 0.60 (0.53, 0.67)| 0.28 (0.19, 0.40)| 0.28 (0.19, 0.40)| 0.56 (0.50, 0.63)| 99.81|< 0.001|
| TIR, Model 3                      | 0.58 (0.52, 0.65)| 0.25 (0.17, 0.37)| 0.25 (0.17, 0.37)| 0.54 (0.48, 0.60)| 127.21|< 0.001|
| TIR, Model 4                      | 0.59 (0.54, 0.66)| 0.28 (0.19, 0.40)| 0.28 (0.19, 0.40)| 0.55 (0.50, 0.62)| 111.33|< 0.001|

Model 1 was adjusted for age, sex, BMI, diabetes duration, SBP, triglyceride, HbA1c and creatinine. 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%). BMI: Body mass index; SD: Standard deviation; TIR: Time in range; UAER: Urinary albumin excretion rate.

Data are presented as mean ± standard deviation or n (%). BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; CV: Coefficient of variation; eGFR: Estimated glomerular filtration rate; HbA1c: Hemoglobin A1c; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; MAGE: Mean amplitude of glycemic excursions; UAER: Urinary albumin excretion rate.

P < 0.001. In multinominal logistic regression model 1, there were significant associations between TIR and microalbuminuria (OR 0.58, 95% CI: 0.52–0.63), P < 0.001 and macroalbuminuria (OR 0.26, 95% CI: 0.18–0.38), P < 0.001 after adjusting for age, sex, BMI, diabetes duration, systolic blood pressure (SBP), and levels of triglycerides, HbA1c and creatinine. Based on model 1, SD (model 2), coefficient of variation (model 3), and mean amplitude of glycemic excursions (model 4) were further adjusted and there was still a significant correlation between TIR and both micro- and macroalbuminuria (all P < 0.001) (Table 2).

Discussion

Among a population of 1014 patients with T2DM, we observed an association between TIR and the severity of UAER. T2DM is often attributed as the cause of end-stage renal disease. Approximately 40% of patients with
T2DM have diabetic kidney disease based eGFR or albuminuria data.\[11,12\] In a large cohort of >4000 patients with type 1 diabetes, the prevalence of microalbuminuria and macroalbuminuria was associated with a 2.80 and 9.20 higher standardized mortality ratio, respectively.\[13\] In a study of 15,046 patients with T2DM, the standardized mortality rate in patients with and without kidney disease was 31.10% and 23.40%, respectively.\[14\] High levels of albuminuria (UAER ≥30 mg/g) are associated with an increased risk of all-cause and cardiovascular mortality independently of declining eGFR and diabetes mellitus.\[15\]

Our results suggest that the proportion of TIR is closely related to early diabetic nephropathy. As diabetic nephropathy developed, the value of TIR decreased. The findings are consistent with clinical trials that have reported a relationship between TIR and the development and progression of diabetic complications. In the Diabetes Control and Complications Trial, the hazard rate for developing retinopathy progression increased by 64% and the development of microalbuminuria increased by 40% for each 10% point decrease in TIR,\[16\] suggesting that TIR is strongly associated with the risk of microvascular complications and should be an acceptable end point for clinical trials. Our results are in line with a study of 3262 T2DM patients in whom TIR assessed by continuous glucose monitoring (CGM) was associated with diabetic retinopathy.\[17\] Similarly, Lu et al\[18\] reported that TIR is associated with carotid intima-media thickness in a study of 2215 patients with T2DM. Hence, TIR is strongly associated with the risk of microvascular complications.

We also found that TIR was significantly associated with the prevalence of UAER after adjusting for HbA1c levels and other clinical risk factors (age, sex, BMI, diabetes duration, systolic blood pressure, and levels of triglycerides and creatinine). According to the quartiles of TIR, the prevalence of both microalbuminuria and macroalbuminuria decreased with ascending quartile of TIR. In the United States, TIR has been recommended as a clinically meaningful outcome beyond HbA1c levels for the research, development, and evaluation of type 1 diabetes.\[19\] For patients with T2DM, regular monitoring of blood glucose plays an important role in controlling their levels. An online survey involving type 1 and type 2 diabetes patients showed that patients believe that diet, exercise, and TIR blood glucose are the biggest drivers of improved diabetes management.\[4\] Together, these findings suggest that TIR adds value as an outcome measure beyond HbA1c levels. Indeed, HbA1c levels do not reflect the fluctuation of blood glucose between individuals,\[20\] and are affected by many clinical conditions (such as anemia and uremia). Patients with similar HbA1c values could have distinct glucose profiles, so HbA1c levels do not reflect the frequency and severity of hyperglycemia and hypoglycemia.\[21\] TIR is not a substitute for HbA1c data, rather, it provides additional information about the quality of overall glycemic control.

Certainly, CGM continuously captures the glucose profile over a number of days and may be the best way to monitor blood glucose status. To date, there is currently very little TIR data obtained via GCM available on diabetic patients. CGM is not widely used in patients with diabetes because of the cost.\[22\] According to data from the T1D Exchange Registry, the utilization rate of CGM was only 7% in 2010–2012 and 30% in 2016–2018.\[23\] In the Diabetes Control and Complications Trial, glycemic data from seven-point fingerstick blood samples were used to validate TIR and clinical outcomes.\[16\] Although the optimal time period over which TIR should be determined for predicting complications risk is currently unknown, it should be recognized that TIR have been assumed to be the same regardless of the CGM device being used.\[22\]

There were some limitations to our study. First, all of our patients were Chinese, and thus our data should not be applied to other ethnic groups. In addition, patient diet during hospitalization could have affect outcomes. Further, we measured blood glucose mostly during the daytime, and thus the calculation of TIR did not include the overnight period. Finally, the observation time of the experiment was too short and the fingerstick blood glucose value collected is limited.

Our study suggests that the short-term blood glucose standard is of great significance in the prevention of early renal function damage. The effect of TIR on UAER is significant for diabetic patients with normal or abnormal eGFR. In conclusion, TIR as assessed using fingerstick samples is negatively associated with the severity of UAER in patients with T2DM.

**Conflicts of interest**

None.

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