Postprint: Correlation Analysis between Time in Range of Glucose and Diabetic Kidney Disease

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Abstract

Background Time in Range (TIR) has emerged in recent years as a novel indicator for glycemic management in diabetes. Studies have confirmed that TIR is closely associated with chronic complications of diabetes. Current research on TIR and diabetic kidney disease (DKD) has primarily focused on albuminuria, often overlooking the role of estimated glomerular filtration rate (eGFR), and there are few studies on the cutoff values of TIR for evaluating glycemic control. Objective To investigate the correlation between TIR and DKD, and to further analyze the cutoff values of TIR for evaluating glycemic control in type 2 diabetes mellitus (T2DM). Methods A total of 214 patients with T2DM hospitalized in the Department of Endocrinology, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine from July 2021 to December 2021 were enrolled. Based on urinary albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) results, the subjects were divided into a pure T2DM group (n=156) and a DKD group (n=58). Inter-group differences were compared and analyzed, and binary logistic regression analysis was used to assess the independent correlation between TIR and DKD. Furthermore, TIR was divided into four groups using 40%, 70%, and 85% as cutoff values, and the distribution trends of clinical data among the four groups were compared and analyzed. Results Compared with the pure T2DM group, patients in the DKD group had a longer duration of diabetes mellitus (DM), higher prevalence of hypertension and systolic blood pressure (SBP), higher levels of uric acid (UA) and triglycerides (TG), poorer glycemic control, greater glycemic variability, and higher proportions of ACEI/ARB, insulin, and GLP-1RA use (all $P<0.05$). Multivariate logistic regression analysis showed that after adjusting for covariates, TIR was independently associated with DKD ($P=0.042$). Further analysis based on different TIR cutoff groupings revealed that with increasing TIR, high-density lipoprotein cholesterol (HDL-C) increased, while glycated hemoglobin (HbA1c), time above range (TAR), and mean glucose (MG) decreased, glycemic variability diminished, and the proportions of insulin and

GLP-1RA use increased (all P<0.05); the detection rate of DKD showed an increasing trend with decreasing TIR (P<0.001). Multivariate logistic regression analysis showed that after adjusting for covariates, compared with the TIR1 group, the risk of DKD detection in the TIR2 group was 1.962 times that of the TIR1 group (P=0.206), the risk in the TIR3 group was 5.287 times that of the TIR1 group (P=0.001), and the risk in the TIR4 group was 4.712 times that of the TIR1 group (P=0.032). Conclusion TIR is independently associated with the risk of DKD, and the incidence of DKD decreases significantly with increasing TIR.

Full Text

Correlation Analysis Between Time in Range and Diabetic Kidney Disease

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Abstract

Background: Time in range (TIR) has emerged as a novel metric for glycemic management in diabetes mellitus. Studies have confirmed that TIR is closely associated with chronic diabetic complications. Current research on TIR and diabetic kidney disease (DKD) has primarily focused on proteinuria, often overlooking the role of estimated glomerular filtration rate (eGFR), and few studies have examined the optimal cut-off points for TIR in evaluating glycemic control.

Objective: To investigate the correlation between TIR and DKD, and to further analyze the appropriate cut-off points for TIR in evaluating glycemic control in type 2 diabetes mellitus (T2DM).

Methods: A total of 214 hospitalized patients with T2DM from the Department of Endocrinology at Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, between July 2021 and December 2021 were enrolled. Based on urinary albumin-to-creatinine ratio (UACR) and eGFR results, participants were divided into a T2DM-only group (n=156) and a DKD group (n=58). Intergroup differences were compared and analyzed. Binary logistic regression was used to analyze the independent correlation between TIR and DKD. Furthermore, TIR was divided into four groups using 40%, 70%, and 85% as cut-off points, and the distribution trends of clinical data among the four groups were compared.

Results: Compared with the T2DM-only group, the DKD group had longer diabetes duration, higher prevalence of hypertension, higher systolic blood pressure (SBP), higher uric acid (UA) and triglyceride (TG) levels, poorer glycemic control, greater glycemic variability, and higher proportions of ACEI/ARB, insulin, and GLP-1RA use (all P<0.05). Multivariate logistic regression analysis showed that TIR was independently associated with DKD after adjusting for covariates (P=0.042). Further grouping by different TIR cut-offs revealed that as TIR increased, HDL-C levels increased while HbA1c, time above range (TAR), and mean glucose (MG) decreased, glycemic variability decreased, and the proportions of insulin and GLP-1RA use increased (all P<0.05). The detection rate of DKD increased with decreasing TIR (P<0.001). Multivariate logistic regression analysis showed that after adjusting for covariates, the risk of DKD in the TIR2 group was 1.962 times that of the TIR1 group (P=0.206), the risk in the TIR3 group was 5.287 times that of the TIR1 group (P=0.001), and the risk in the TIR4 group was 4.712 times that of the TIR1 group (P=0.032).

Conclusion: TIR is independently correlated with the risk of DKD. As TIR increases, the incidence of DKD decreases significantly. Using 40%, 70%, and 85% as cut-off points for TIR classification can effectively distinguish the risk of DKD.

Keywords: time in range; type 2 diabetes mellitus; diabetic kidney disease; early prevention

Introduction

Diabetic kidney disease (DKD) is one of the chronic complications of diabetes mellitus, a form of chronic kidney disease (CKD) caused by diabetes, characterized by persistently increased albuminuria excretion and/or progressive decline in glomerular filtration rate (GFR), which can ultimately progress to end-stage renal disease (ESRD) [1]. Poor glycemic control is an independent risk factor for the development of albuminuria and/or progression to ESRD [2], and the occurrence and development of DKD are closely related to glycemic control status. For diabetic patients with suboptimal glycemic control, early intensive glycemic control is beneficial for reducing the risk of diabetic complications [3,4]. Currently, glycated hemoglobin (HbA1c) is primarily used as the "gold standard" for glycemic control, but in clinical practice, HbA1c has limitations in that it cannot reflect immediate glucose levels or glycemic variability [5,6]. Shrom et al. [7] also found that HbA1c does not consistently reflect mean plasma glucose levels in some patients. Additionally, HbA1c is affected by age, hematologic disorders, pregnancy, chronic kidney disease, and liver disease [8]. Therefore, how to more comprehensively evaluate the quality of glycemic control has attracted attention. The recent emergence of TIR as a new metric for glycemic management provides a solution to this problem. Within a certain range, TIR can effectively predict fluctuations in HbA1c [9,10], and moreover, TIR can re-

flect immediate glucose levels and glycemic variability, providing more specific, comprehensive, and complete glucose information for early glycemic control in diabetic patients.

Previous studies on the relationship between TIR and DKD have mainly focused on the risk of albuminuria, often neglecting the value of glomerular filtration rate (GFR) in diagnosing DKD. A large cross-sectional study evaluating T2DM patients from 33 countries found that the overall prevalence of albuminuria was 49%, while the prevalence of eGFR <60 ml/min/1.73m^2 was approximately 22%, both of which were associated with the risk of kidney disease [11]. However, albuminuria and eGFR decline are not completely correlated. Zhao et al. [12] found that there was no statistically significant correlation between microalbuminuria and eGFR in T2DM patients, and that urinary microalbumin could not fully reflect changes in eGFR. Lu et al. [13] conducted a 5-year follow-up study of 102 T2DM patients in the community and found that approximately 43.9% of patients had non-parallel progression of urinary protein excretion rate and eGFR. Therefore, this study used both UACR and eGFR as grouping criteria for DKD to more accurately reflect the relationship between TIR and DKD, aiming to provide a theoretical basis for the early prevention of DKD occurrence and development.

Methods

Study Population

A total of 214 patients with T2DM hospitalized in the Department of Endocrology at Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine from July 2021 to December 2021 were enrolled. The study was approved by the Medical Ethics Committee of Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (Ethics Approval No.: XHEC-D-2022-087), and all participants provided informed consent.

Inclusion Criteria

1. Age $ $18 years
2. Diagnosis of diabetes according to 1999 World Health Organization (WHO) criteria
3. Complete clinical data available
4. Informed consent obtained

Exclusion Criteria

1. Other types of diabetes
2. Severe liver or kidney damage, or other diseases that may cause proteinuria or decreased GFR (such as malignant tumors, hematologic disorders, rheumatic immune diseases)

3. Recent major trauma, fracture, surgery, infection, or other acute stress states, or recent cardiovascular/cerebrovascular events such as acute myocardial infarction, heart failure, or stroke
4. Recent use of nephrotoxic drugs, or medications affecting GFR such as diuretics or uric acid-lowering agents
5. Recent acute diabetic complications

Research Methods

Patient information including sex, age, diabetes duration, hypertension status, and medication use was collected from admission records. Blood pressure (mmHg), height (m), weight (kg), and waist circumference (cm) were recorded at admission. Blood pressure was measured by designated personnel using the same electronic sphygmomanometer model. Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2). All participants were on regular medication; fasting peripheral venous blood samples (after 8-12 hours of fasting) were collected the morning after admission. Serum uric acid (UA), serum creatinine (Scr), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured using an automatic biochemical analyzer (Model 7104, Hitachi, Japan). HbA1c was measured by high-performance liquid chromatography (HA-8150, Arkray, Japan). eGFR was calculated by the laboratory using the Modification of Diet in Renal Disease (MDRD) formula: eGFR = 175 × (Scr/88.4)^(-1.234) × age^(-0.179) ($×$0.79 for females). Random urine samples were collected, and urinary albumin-to-creatinine ratio (UACR) was determined by immunoturbidimetry. All enrolled participants were fitted with a retrospective continuous glucose monitoring (CGM) system by endocrinologists, received standardized diets, and underwent 72 hours of continuous subcutaneous interstitial glucose monitoring. After monitoring, TIR, time above range (TAR), time below range (TBR), mean glucose (MG), standard deviation of blood glucose (SDBG), mean amplitude of glycemic excursion (MAGE), coefficient of variation (CV), and largest amplitude of glycemic excursion (LAGE) were calculated.

Grouping Methods

According to the Chinese Clinical Practice Guideline for Diabetic Kidney Disease [1], participants were divided into a DKD group (UACR $ $30mg/gandoreGFR < 60ml/min/1.73m^{2}$) and a T2DM-only group (UACR <30 mg/g and eGFR $ $60ml/min/1.73m^{2}$) based on UACR and eGFR levels. UACR was further categorized into normal (UACR <30 mg/g) and abnormal (UACR $ $30 mg/g) groups. Based on Dai et al.' s [14] analysis of appropriate cut-off points for TIR in evaluating glycemic control in T2DM, TIR was divided into four groups using 40%, 70%, and 85% as cut-off points: TIR1 group (TIR >85%), TIR2 group (70% < TIR $ $85%), TIR3 group (40% < TIR $ $70%), and TIR4 group (TIR $ $40%).

Statistical Methods

Data analysis was performed using SPSS 26.0 statistical software. Continuous variables with normal distribution were expressed as mean ± standard deviation ($\bar{x}\pm s$), non-normally distributed continuous variables as median (interquartile range) [M(P25,P75)], and categorical data as number (percentage) [n(%)]. For comparisons between two groups, t-tests were used for normally distributed continuous variables with homogeneity of variance, non-parametric rank-sum tests for normally distributed but heteroscedastic or non-normally distributed continuous variables, and chi-square tests for categorical data. Trend tests for normally distributed continuous variables used ANOVA linear trend analysis, non-normally distributed continuous variables used Jonckheere-Terpstra test, and categorical data used Cochran-Armitage trend test. Correlations between two variables were analyzed using Spearman correlation analysis. Binary logistic regression was used to assess the independent correlation between TIR and DKD. $P<0.05$ was considered statistically significant.

Results

Clinical Characteristics of Study Participants

A total of 214 T2DM patients were enrolled, with 60.7% male (n=130) and 39.3% female (n=84), mean age (63.3$±10.2)$years, and mean diabetes duration (12.8±$8.3) years. Participants were divided into T2DM-only and DKD groups. The distribution of clinical characteristics is shown in Table 1 . Statistically significant differences between groups were observed in diabetes duration, hypertension prevalence, hypertension duration, SBP, UA, TG, HDL-C, HbA1c, TIR, TAR, MG, SDBG, LAGE, ACEI/ARB use, insulin use, and GLP-1RA use ($P<0.05$). No significant differences were found in age, sex, DBP, BMI, waist circumference, smoking history, alcohol history, Scr, TC, LDL-C, TBR, MAGE, CV, statin use, non-statin lipid-lowering drug use, or oral hypoglycemic agent use ($P>0.05$).

Logistic Regression Analysis of TIR and DKD

Using DKD risk presence (assignment: yes=1, no=0) as the dependent variable and TIR (assignment: actual value) as the independent variable, multivariate logistic regression analysis was performed after adjusting for covariates (sex, age, diabetes duration, hypertension prevalence, hypertension duration, Scr, UA, BMI, SBP, TG, HDL-C, HbA1c, SDBG, LAGE, ACEI/ARB use, insulin use, and GLP-1RA use). The results showed that TIR was an influencing factor for DKD risk [OR=0.976, 95%CI (0.953,0.999), P=0.042].

Subgroup analysis revealed that TIR was significantly associated with DKD in populations not using ACEI/ARB drugs, while no statistically significant correlation was found in those using these medications (see Table 2).

Distribution of Clinical Characteristics by TIR Groups

When participants were further divided into four groups based on TIR levels, the distribution of clinical characteristics is shown in Table 3 . Significant differences were observed among the four groups in diabetes duration, HDL-C, HbA1c, eGFR, abnormal UACR, TAR, MG, SDBG, MAGE, LAGE, CV, insulin use, and GLP-1RA use (all trend P<0.05). No significant differences were found in hypertension prevalence, SBP, DBP, BMI, waist circumference, Scr, UA, TC, TG, LDL-C, eGFR, TBR, ACEI/ARB use, statin use, non-statin lipid-lowering drug use, or oral hypoglycemic agent use (all trend P>0.05).

Distribution of DKD Across TIR Groups

Among the study population, 58 patients (27.1%) were classified into the DKD group. The prevalence of DKD showed a gradually increasing trend with decreasing TIR: 12.2% (11/90) in TIR1 group, 23.5% (12/51) in TIR2 group, 47.4% (27/57) in TIR3 group, and 50.0% (8/16) in TIR4 group (trend P<0.001) (see Figure 1 [Figure 1: see original paper]).

Distribution of Mean eGFR Across TIR Groups

The overall mean eGFR in the study population was 107.2$±26.9$mL/min/1.73m^{2}$.ThemeaneGFRacrossgroupssho in TIR1 group, 118.9$±24.3$mL/min/1.73m^{2}$ in TIR2 group, 102.3$±30.2$mL/min/1.73m^{2}$ in TIR3 group, and 88.3$±31.3$mL/min/1.73m^{2}$ in TIR4 group (trend P<0.001) (see Figure 2 [Figure 2: see original paper]).

Logistic Regression Analysis of TIR Groups and DKD Risk

Using DKD risk presence (assignment: yes=1, no=0) as the dependent variable and TIR group [assignment: TIR1 group (TIR>85%)=1, TIR2 group (70%<TIR$ 85 70 $40%)=4] as the independent variable, binary logistic regression analysis without adjustment showed that compared with TIR1 group, the risk of DKD in TIR2 group was 2.210 times [OR=2.210, 95%CI (0.895,5.455), P=0.085], in TIR3 group was 6.464 times [OR=6.464, 95%CI (2.854,14.638), P<0.001], and in TIR4 group was 7.182 times [OR=7.182, 95%CI (2.239,23.034), P=0.001] (trend P<0.001). After adjusting for sex, age, diabetes duration, BMI, hypertension prevalence, LDL-C, SDBG, ACEI/ARB use, and GLP-1RA use, multivariate logistic regression analysis showed that compared with TIR1 group, the risk of DKD in TIR2 group was 1.962 times [OR=1.962, 95%CI (0.690,5.578), P=0.206], in TIR3 group was 5.287 times [OR=5.287, 95%CI (1.897,14.737), P=0.001], and in TIR4 group was 4.712 times [OR=4.712, 95%CI (1.143,19.424), P=0.032] (trend P=0.010) (see Table 4).

Discussion

This study simultaneously incorporated both UACR and eGFR in the analysis of DKD groups and TIR. The results showed that compared with the T2DM-only group, DKD patients had longer diabetes duration and hypertension duration, higher hypertension prevalence and SBP, higher UA and TG levels, poorer glycemic control (higher HbA1c, TAR, and MG; lower TIR), greater glycemic variability (higher SDBG and LAGE), and higher proportions of ACEI/ARB, insulin, and GLP-1RA use. Multivariate logistic regression analysis demonstrated that TIR was independently associated with DKD risk after adjusting for confounding factors. To exclude the effect of ACEI/ARB drugs on proteinuria, subgroup analysis found that TIR was significantly correlated with DKD in populations not using ACEI/ARB drugs, while no statistically significant correlation was observed in those using these medications, which is related to the albuminuria-reducing effect of ACEI/ARB drugs.

Further analysis using 40%, 70%, and 85% as TIR cut-off points revealed that patients with higher TIR had shorter diabetes duration, higher HDL-C levels, better glycemic control (lower HbA1c, TAR, and MG), smaller glycemic variability (lower SDBG, MAGE, LAGE, and CV), and lower proportions of insulin and GLP-1RA use. With decreasing TIR, the risk of DKD increased significantly. Multivariate logistic regression analysis showed that after adjusting for confounders, compared with TIR1 group, the risk of DKD in TIR2 group was 1.962 times (P=0.206), in TIR3 group was 5.287 times (P=0.001), and in TIR4 group was 4.712 times (P=0.032) that of TIR1 group (trend P=0.010). These results indicate that in patients with type 2 diabetes, TIR can simultaneously reflect both glycemic control level and glycemic variability. As TIR increases, the risk of DKD decreases significantly. Using 40%, 70%, and 85% as cut-off points for TIR classification can effectively distinguish the risk of DKD.

Previous studies have reported that TIR is closely related to the occurrence and development of DKD. Beck et al. [15] found that TIR was significantly associated with microalbuminuria, with each 10% decrease in TIR increasing the risk of microalbuminuria by 40%. Yoo et al. [8] confirmed this conclusion, demonstrating that TIR was independently associated with albuminuria after adjusting for covariates (age, sex, BMI, SBP, TG, LDL-C, ACEI/ARB use, SGLT-2i use, CKD, diabetes duration, and CV). In contrast, this study considered both albuminuria and eGFR in DKD diagnosis, providing a more comprehensive illustration of the independent correlation between TIR and DKD. The 2019 International Consensus on TIR [16] proposed TIR >70% as the glycemic control target for diabetic patients. However, most current studies have used TIR quartile grouping to evaluate the risk of diabetic complications, but since TIR distribution varies across different study populations, the quartiles often differ. Therefore, how to specifically define TIR cut-off points warrants further investigation. Dai et al. [14] found that using 40%, 70%, and 85% as TIR cut-off points could effectively differentiate the risk of abnormal carotid intima-media thickness (CIMT) and diabetic retinopathy (DR) in T2DM patients, proposing

these values as cut-off points for "poor," "target," and "excellent" glycemic control. This study further explored the correlation between TIR and DKD risk using these cut-off points. The results showed that compared with TIR1 group (TIR>85%), the risk of DKD in TIR2 group (70%≤TIR<85%) was not statistically significant, suggesting that future research is needed to determine the cut-off point for "excellent" glycemic control.

Analysis of eGFR distribution across different TIR groups showed that eGFR increased between TIR1 and TIR2 groups. The possible reason is that in patients with good glycemic control (TIR>70%), microvascular lesions caused by glucose metabolism disorders have less impact on eGFR, while elevated blood glucose can increase plasma osmotic pressure, leading to increased eGFR. From TIR2 to TIR4 groups, eGFR showed a downward trend, indicating that when glycemic control is chronically inadequate (TIR<70%), microvascular lesions from glucose metabolism disorders become more severe, resulting in a significant decline in eGFR. This study found that in TIR grouping Model 4, the risk in TIR4 group was lower than in TIR3 group, possibly due to the significantly higher proportion of GLP-1RA use with decreasing TIR. Meta-analysis has shown that GLP-1RA can reduce the risk of composite kidney endpoints (new-onset macroalbuminuria, decreased GFR, ESRD, death) by 17% [17].

The exact mechanism underlying the correlation between TIR and DKD has not been established in this study, but hyperglycemia, glycemic variability, and lipid disorders may be responsible. Hyperglycemia can reduce the number and impair the function of endothelial progenitor cells (EPCs) in diabetic patients through multiple pathways, causing vascular endothelial cell injury. It affects vascular endothelial cell function through mechanisms such as polyol pathway activation, increased advanced glycation end-product formation, and protein kinase C activation, exacerbating diabetic vascular lesions [18,19]. Glycemic variability primarily activates oxidative stress, damages endothelial cells, aggravates inflammatory changes, thereby causing vascular injury and increasing the risk of diabetic complications [20]. Lipid accumulation can induce oxidative stress, release inflammatory factors and growth factors, leading to glomerular injury [21]. Additionally, lipoproteins can competitively inhibit plasmin activity, cause intrarenal vascular thrombosis, aggravate renal ischemia and hypoxia, and cause tubular injury. Hyperlipidemia can also worsen insulin resistance, cause hyperinsulinemia, and indirectly damage the kidneys through angiotensin II [22]. This study showed that higher TIR was associated with lower hyperglycemia levels, less glycemic variability, and higher HDL-C levels. Therefore, maintaining TIR at a higher level can effectively reduce the risk of DKD.

This study confirms that TIR is independently correlated with DKD, and using 40%, 70%, and 85% as cut-off points for TIR classification can effectively distinguish DKD risk. Higher TIR can effectively reduce the risk of DKD. In conclusion, while routinely performing HbA1c testing, monitoring TIR can more comprehensively reflect glycemic control status and help with early intensive glycemic control and early prevention of DKD.

This study has several limitations. First, as a single-center study with a small sample size, particularly few samples with eGFR <60 ml/min/1.73m^2, it was unable to deeply investigate the association between TIR and eGFR decline. Second, as a retrospective study, it could not track the causal relationship between TIR and DKD development. Third, participants received standardized diets during CGM monitoring as inpatients, which may not reflect their glycemic status under usual dietary conditions. Fourth, the TIR International Consensus [16] states that 14 days of CGM data better reflects long-term glycemic control, while this study used 3 days of CGM monitoring, which may require longer monitoring for further validation. Additionally, although CGM technology may not be widely available in some primary care settings, studies have shown [23] that TIR calculated from seven-point blood glucose measurements is also associated with diabetic complications. Future research in primary care settings using fingerstick blood glucose measurements could expand the use of TIR in early prevention of diabetic complications. Therefore, future multi-center, large-sample, prospective studies are needed to confirm these findings.

Author Contributions

Shu Tao contributed to conception and design, data management, statistical analysis, results interpretation, and manuscript writing, and takes overall responsibility for the article. Shu Tao and Guo Zheng contributed to data collection and organization. Shu Tao, Guo Zheng, and Chen Shuyan contributed to study implementation and feasibility analysis. Shu Tao, Wang Fei, and Chen Shuyan contributed to manuscript revision, quality control, and supervision.

Conflict of Interest: The authors declare no conflicts of interest.

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Note: Figure translations are in progress. See original paper for figures.