Time in Range and Long-term Glycemic Variability in Elderly Male Patients with Type 2 Diabetes Mellitus: A Postprint

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Abstract

Background: Time in Range (TIR), as a novel metric for glycemic management, is associated with short-term glycemic fluctuations; however, its relationship with long-term glycemic variability remains unclear. Objective: To investigate the association between TIR and both the coefficient of variation of glycated hemoglobin (HbA1c) and the HbA1c variability score (HVS) during long-term follow-up in elderly male patients with type 2 diabetes mellitus. Methods: A total of 200 elderly male patients with type 2 diabetes mellitus who underwent continuous glucose monitoring (CGM) as inpatients at the Second Medical Center of the Chinese PLA General Hospital between January 2007 and January 2011 were selected. Based on baseline TIR levels, patients were divided into a TIR$ 85±1.1)$years, and the coefficient of variation of HbA1c and HVS during long-term follow-up were compared between the two groups. Pearson correlation analysis and multiple linear arregressio The long-term HbA1c coefficient of variation [(9.7±3.8)±4.5)±20.4)$points vs.$(32.5±20.8)$points, P < 0.001] were significantly higher in the $TIR < 85$ $85% group. Pearson correlation analysis revealed that TIR was linearly and negatively correlated with long-term HbA1c coefficient of variation (r=-0.239, P<0.001) and HVS (r=-0.400, P<0.001). Multiple linear regression analysis demonstrated that after adjusting for confounding factors, TIR had a significant effect on long-term HbA1c coefficient of variation and HVS [b (95%CI): -0.07 (-0.12, -0.03) and -0.44 (-0.67, -0.21), respectively, P<0.05]. Conclusion: In elderly male patients with type 2 diabetes mellitus, TIR is associated with HbA1c coefficient of variation and HVS during long-term follow-up. Lower TIR is associated with more pronounced long-term glycemic variability.

Full Text

Relationship between Time in Range and Long-term HbA1c Glycemic Variability in Elderly Male Patients with Type 2 Diabetes

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Abstract

Background As a new indicator of glycemic management, time in range (TIR) is significantly related to short-term glycemic variability, but whether it is also associated with long-term glycemic variability remains unclear. **Objective** To investigate the relationship of TIR with coefficient of variability (CV) of HbA1c and HbA1c variability score (HVS) during long-term follow-up in elderly male patients with type 2 diabetes. **Methods** Two hundred elderly male type 2 diabetic inpatients who underwent continuous glucose monitoring (CGM) at the Second Medical Center of PLA General Hospital between January 2007 and January 2011 were enrolled. Based on baseline TIR levels, patients were divided into TIR $\geq$ 85% group (n=141) and TIR $<$ 85% group (n=59). All participants were followed for $(12.5\$\pm1.1)years, and CV of HbA1c and HVS were compared between groups. Pearson correlation analysis and mu$
$*Results**The long-term CV of HbA1c[(9.7\pm3.8)\pm4.5)\pm20.4)vs(32.5\pm\$20.8)$, P<0.001] in the TIR $<$ 85% group were significantly higher than those in the TIR $\geq$ 85% group. Pearson correlation analysis showed that TIR had a significant linear negative correlation with CV of HbA1c (r=-0.239, P<0.001) and HVS (r=-0.400, P<0.001). Multiple linear regression analysis indicated that TIR independently affected long-term CV of HbA1c [b (95%CI) = -0.07 (-0.12, -0.03), P<0.05] and HVS [b (95%CI) = -0.44 (-0.67, -0.21), P<0.05] after adjusting for confounding factors. **Conclusion** TIR was independently associated with long-term CV of HbA1c and HVS in elderly male patients with type 2 diabetes. Lower TIR was associated with more pronounced long-term glycemic variability.

Keywords Diabetes mellitus, type 2; Time in range; Glycemic variability; Glycosylated hemoglobin; Continuous glucose monitoring; Aged; Men

Introduction

With the widespread application of continuous glucose monitoring (CGM) technology in diabetes management, time in range (TIR) has emerged as a novel metric for glycemic control. TIR provides a more comprehensive reflection of short-term glycemic status and is characterized by its simplicity and intuitive interpretation, garnering extensive attention in the field [1]. Previous studies have demonstrated that TIR correlates linearly with glycated hemoglobin (HbA1c) levels and can reflect short-term glycemic fluctuations [2]. However, whether TIR is associated with long-term glycemic variability remains unclear. This study conducted long-term follow-up of elderly male patients with type 2 diabetes who underwent CGM to explore the relationship between TIR and long-term HbA1c variability, thereby providing additional evidence for using TIR as a glycemic management indicator in elderly diabetic populations.

Methods

Study Subjects

We enrolled 200 elderly male patients with type 2 diabetes who were hospitalized and underwent CGM at the Second Medical Center of Chinese PLA General Hospital between January 2007 and January 2011. Inclusion criteria were: (1) age $\geq$ 60 years; (2) male sex; (3) diagnosis of diabetes according to 1999 WHO criteria [3]; and (4) stable antihyperglycemic regimen for 1 month before CGM. Exclusion criteria included: (1) other types of diabetes; (2) use of glucocorticoids or other medications affecting glucose metabolism; and (3) severe hepatic or renal insufficiency. This study was approved by the Ethics Committee of Chinese PLA General Hospital (approval No. S2015-038-01), complied with the Declaration of Helsinki, and all participants provided informed consent.

Baseline Data Collection

A standardized information form was used to retrospectively collect baseline data. General information included age, height, weight, diabetes duration, blood pressure, medication use, and BMI. Laboratory measurements comprised fasting plasma glucose (FPG), 2-hour postprandial glucose (2hPG) measured by glucose oxidase method; HbA1c measured by high-performance liquid chromatography (Variant II analyzer); and total cholesterol (TC), triglycerides (TG), LDL-C, and HDL-C measured by enzymatic methods. CGM parameters were obtained using a Medtronic CGM system (MMT-7102) for 3 consecutive days, with data from two complete 24-hour periods used to calculate mean amplitude of glycemic excursion (MAGE), glucose coefficient of variation, and TIR. TIR was defined as the percentage of time with glucose levels between 3.9-10.0 mmol/L over 24 hours. Based on baseline TIR levels and previous studies, patients were categorized into TIR $\geq$ 85% and TIR $<$ 85% groups [4].

Follow-up

All patients were followed until November 2021, with a mean follow-up duration of (12.5$±$1.1) years. No interventions were performed during follow-up; patients continued receiving routine medical care. All HbA1c measurements during follow-up were collected from electronic medical records. Long-term HbA1c variability was assessed using HbA1c coefficient of variation and HbA1c variability score (HVS). HbA1c coefficient of variation was calculated as (standard deviation ÷ mean) × 100%. HVS was calculated as the percentage of adjacent HbA1c differences ≥ 0.5% relative to total comparisons [5].

Statistical Analysis

Data were organized using Excel and analyzed with SPSS 17.0. Normally distributed continuous variables were expressed as (x-±s) and compared between groups using independent samples t-test. Categorical variables were expressed as percentages and compared using ^{2} test. Pearson correlation analysis examined relationships between TIR and long-term HbA1c variability indices. Univariate and multivariate linear regression analyses assessed the impact of TIR on long-term HbA1c variability. P<0.05 was considered statistically significant.

Results

Comparison of Baseline Characteristics

Among 200 elderly male patients with type 2 diabetes, 59 (29.5%) were in the TIR < 85% group and 141 (70.5%) in the TIR ≥ 85% group. The TIR < 85% group had significantly higher baseline age, BMI, diabetes duration, FPG, 2hPG, HbA1c, MAGE, and glucose coefficient of variation, as well as higher insulin use (P<0.05). No significant differences were observed in systolic blood pressure, diastolic blood pressure, TC, TG, LDL-C, HDL-C, or use of metformin or sulfonylureas (P>0.05) .

Comparison of HbA1c Measurements and Long-term Variability During Follow-up

There was no significant difference in the number of HbA1c measurements between groups (P>0.05). However, HbA1c mean, HbA1c coefficient of variation, and HVS differed significantly (P<0.05) .

Correlation Analysis Between TIR and Long-term HbA1c Variability

Pearson correlation analysis revealed that TIR was negatively correlated with HbA1c mean (r=-0.395, P<0.001), HbA1c coefficient of variation (r=-0.239, P<0.001), and HVS (r=-0.400, P<0.001).

Linear Regression Analysis of TIR Impact on Long-term HbA1c Variability

Using HbA1c mean, HbA1c coefficient of variation, and HVS as dependent variables and TIR as the independent variable, univariate linear regression showed TIR significantly affected all three outcomes [b (95%CI): -0.02 (-0.03, -0.01), -0.06 (-0.10, -0.03), and -0.55 (-0.72, -0.37), respectively; P<0.05]. After adjusting for age, BMI, diabetes duration, FPG, MAGE, and insulin use, multivariate linear regression confirmed TIR independently affected HbA1c mean [b (95%CI) = -0.01 (-0.02, 0.00)], HbA1c coefficient of variation [b (95%CI) = -0.07 (-0.12, -0.03)], and HVS [b (95%CI) = -0.44 (-0.67, -0.21)] (P<0.05) .

Sensitivity Analysis

During follow-up, 90 patients (45.0%) died and 7 (3.5%) were lost to follow-up. After excluding these cases, the effect of TIR on long-term HbA1c variability remained consistent with the main analysis. TIR continued to significantly affect HVS [b (95%CI) = -0.41 (-0.77, -0.04)], though its impact on HbA1c mean and coefficient of variation was no longer significant (P>0.05) .

Discussion

Current research has established that TIR is closely associated with diabetic chronic complications. TIR correlates with the prevalence and severity of diabetic retinopathy, with lower TIR and greater glycemic fluctuations associated with more severe retinopathy [6]. MALAHİ et al. [7] found that TIR, but not glycemic variability, was associated with microvascular complications in type 1 diabetes. LU et al. [8] followed patients with type 2 diabetes for a mean of 6.9 years and found TIR was significantly associated with increased risks of all-cause and cardiovascular mortality. The 2017 International Consensus on CGM and the 2020 American Diabetes Association guidelines recommend TIR as a key metric in CGM reports and diabetes management [9]. TIR is closely related to other glycemic control indicators. Vigersky and McMahon [2] reviewed 18 randomized controlled trials and found a linear negative correlation between TIR and HbA1c (r=-0.84, R^2=0.71). BECK et al. [10] reviewed four randomized controlled trials and found that TIR in type 1 diabetes was highly correlated with mean glucose and moderately correlated with HbA1c, while also being closely associated with short-term glycemic variability indices such as MAGE and coefficient of variation [11]. However, studies analyzing the relationship between TIR and long-term glycemic variability are lacking. Our cohort of elderly male patients with relatively stable glycemic control used TIR >85% as the cutoff for optimal control based on previous research [4]. We found that TIR was linearly associated with long-term HbA1c coefficient of variation and HVS, with decreasing TIR associated with increasing HbA1c coefficient of variation and HVS, indicating more pronounced long-term glycemic variability.

Long-term glycemic variability reflects glucose fluctuations over months to years,

primarily manifested as HbA1c variability during follow-up. Most studies have used HbA1c coefficient of variation and standard deviation to assess long-term glycemic variability. MAO et al. [13] found that HbA1c coefficient of variation was an independent risk factor for microvascular complications in type 1 diabetes. An observational study using HbA1c standard deviation and coefficient of variation found that HbA1c variability was associated with increased risks of all-cause mortality, cardiovascular death, and diabetic complications [14]. However, these metrics are not easily interpretable in clinical practice. Recently, HVS has been proposed to evaluate long-term glycemic variability [5,15], representing the proportion of adjacent HbA1c measurements differing by $ $0.5%. LI et al. [16] found that HVS, independent of HbA1c, was associated with increased risks of all-cause mortality, cardiovascular events, and microvascular complications in newly diagnosed type 2 diabetes. MAO et al. [17] followed 15,286 patients with diabetes and found that HVS and obesity were associated with increased risks of all-site cancer and cancer-related mortality.

Current guidelines recommend TIR as a novel and useful glycemic management indicator. HbA1c remains the primary metric for glycemic control [18], but it has limitations [19-20]. Our study found that TIR in elderly patients with type 2 diabetes was associated with long-term HbA1c mean and could reflect long-term glycemic variability, supporting TIR as an effective complement to HbA1c. CGM provides continuous monitoring of interstitial glucose levels, offering comprehensive and reliable glucose information [21]. While CGM metrics such as MAGE and coefficient of variation can quantify glycemic fluctuations and are widely used clinically and in research, they are difficult for patients to understand. TIR is simple, intuitive, and comprehensible, correlating not only with short-term glycemic control and fluctuations but also effectively reflecting long-term glycemic variability. This helps clinicians predict future long-term glycemic variability and facilitates self-management in elderly patients with type 2 diabetes.

In summary, this study of elderly male patients with type 2 diabetes who underwent CGM demonstrated that TIR is associated with long-term glycemic variability, with lower TIR associated with more pronounced HbA1c variability. Therefore, TIR not only reflects short-term glycemic control and fluctuations but also correlates significantly with long-term glycemic variability. During management of elderly type 2 diabetes, TIR may help predict future glycemic variability and facilitate long-term glycemic management. This study has limitations: the cohort comprised elderly males with relatively stable glycemic control and a small sample size. Thus, this is a preliminary exploratory study, and the findings require confirmation in multi-center, large-scale prospective studies.

Author Contributions: FANG Fusheng conceived the study, designed the protocol, performed statistical analysis, drafted the manuscript, and interpreted the results. LIU Xingyu, YAN Shuangtong, and WANG Ning conducted the research, collected data, and performed literature searches. LI Chunlin and

TIAN Hui designed the study, supervised the research, and provided quality control and revision of the manuscript.

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

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