Correlation Between Time in Range and Long-term Glycemic Variability in Elderly Men with Type 2 Diabetes: A Postprint

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Abstract

Background Time in Range (TIR) serves as a new metric for glycemic management and is associated with short-term glycemic fluctuations; however, its relationship with long-term glycemic variability remains unclear.

Objective To investigate the correlation between TIR and HbA1c coefficient of variation as well as HbA1c variability score during long-term follow-up in elderly male patients with type 2 diabetes mellitus.

Methods The study enrolled 200 elderly male patients with type 2 diabetes mellitus who underwent continuous glucose monitoring during hospitalization at the Second Medical Center of Chinese PLA General Hospital from January 2007 to January 2011. Participants were divided into two groups based on TIR levels and followed up for 12.5 years. Differences in HbA1c coefficient of variation and HbA1c variability score during long-term follow-up were compared between the two groups. Multivariate linear regression analysis was used to analyze the correlation between TIR and HbA1c coefficient of variation as well as HbA1c variability score.

Results The TIR <85% group exhibited significantly higher HbA1c coefficient of variation (9.70$±3.82±4.45±20.4*vs*.32.5±$20.9, P<0.001) compared to the TIR $ 85 = −0.07, 95{2}= 0.100)*and**HbA1cvariabilityscore*(= −0.44, 95{2}$=0.234) during long-term follow-up.

Conclusion In elderly male patients with type 2 diabetes mellitus, TIR is independently associated with HbA1c coefficient of variation and HbA1c variability score during long-term follow-up. Patients with lower TIR demonstrate more pronounced long-term glycemic variability.

Full Text

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

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Abstract

Background: Time in range (TIR) has emerged as a novel metric for glycemic management that is significantly related to short-term glycemic variability, though its association with long-term glycemic variability remains unclear.

Objective: To investigate the relationship between TIR and both HbA1c coefficient of variation (CV) and HbA1c variability score (HVS) during long-term follow-up in elderly male patients with type 2 diabetes.

Methods: A total of 200 elderly male patients with type 2 diabetes who underwent continuous glucose monitoring (CGM) were enrolled from January 2007 to January 2011 at the Second Medical Center of PLA General Hospital. Participants were divided into two groups according to TIR level and followed for 12.5 years. Between-group differences in HbA1c CV and HVS were compared during follow-up, and multivariate linear regression analysis was used to assess the relationship between TIR and both HbA1c CV and HVS.

Results: The TIR<85% group exhibited significantly higher HbA1c CV ($9.70\$\pm3.82\pm4.45\pm20.4 vs. 32.5\pm20.9, P < 0.001$) *compared to the* $TIR\ 85 = -0.07, 95^{\{2\}= 0.100)}$ *and* $HVS(= -0.44, 95\{2\}\$=0.234)$ during long-term follow-up.

Conclusion: In elderly male patients with type 2 diabetes, TIR is independently associated with both HbA1c CV and HVS during long-term follow-up. Lower TIR values are associated with more pronounced long-term glycemic variability.

Keywords: Elderly; Type 2 diabetes; Time in range; Glycosylated hemoglobin; Glycemic variability

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 that provides a more comprehensive reflection of short-term glucose profiles. Its simplicity and intuitive nature have garnered considerable attention. Previous studies have established a strong linear relationship between TIR and glycosylated hemoglobin (HbA1c) and have demonstrated its ability to reflect short-term glycemic fluctuations. However, whether TIR is associated with long-term glycemic variability remains unknown. This study investigated the relationship between TIR and HbA1c variability through long-term follow-up of elderly patients with type 2 diabetes who underwent CGM.

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1. Subjects and Methods

1.1 Study Subjects We enrolled 200 elderly male patients with type 2 diabetes who were hospitalized for CGM between January 2007 and January 2011 at the Second Medical Center of PLA General Hospital. Inclusion criteria were: age $ $60 years; diagnosis of diabetes according to 1999 WHO criteria; and stable antihyperglycemic treatment regimen for one month prior to CGM. Exclusion criteria included other types of diabetes and use of glucocorticoids or other medications that might affect glucose metabolism. The study was approved by the Ethics Committee of Chinese PLA General Hospital (approval number: S2015-038-01) and complied with the Declaration of Helsinki.

1.2 Research Methods Baseline clinical data were retrospectively collected, including: (1) general information: age, height, weight, blood pressure, with body mass index (BMI) calculated as weight (kg) divided by height (m) squared; (2) laboratory measurements: fasting plasma glucose (FPG) and 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), high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c) measured by enzymatic methods; and (3) CGM parameters: using Medtronic CGM systems (MMT-7102) for 3 consecutive days to calculate mean amplitude of glycemic excursion (MAGE), coefficient of variation (CV), and TIR, defined as the percentage of time glucose remained within 3.9-10.0 mmol/L over 24 hours. Participants were stratified into two groups based on TIR level: TIR$ $85% and TIR<85%.

All subjects were followed until November 2021 without any intervention. During follow-up, participants continued to receive routine medical care, and all HbA1c measurements from clinical visits were collected and verified through electronic medical records. Long-term glycemic variability was assessed using

HbA1c CV and HbA1c variability score (HVS). HVS was calculated using all baseline and follow-up HbA1c values as: HVS = (number of adjacent HbA1c differences $ $0.5% / total number of adjacent HbA1c comparisons) × 100.

1.3 Statistical Methods Data were organized using Excel and analyzed with SPSS 17.0 software. Complete 24-hour CGM data from two days were used to calculate glycemic variability indices. The mean follow-up duration was 12.5 years, during which 90 participants (45.0%) died and 7 (3.5%) were lost to follow-up. Continuous variables are expressed as mean±standard deviation, and categorical variables as number (percentage). Between-group comparisons of continuous variables used t-tests, while chi-square tests compared rates. Pearson correlation analysis assessed relationships between continuous variables, and univariate and multivariate linear regression analyses examined associations between TIR and HbA1c CV or HVS. Statistical significance was defined as $P<0.05$.

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2. Results

2.1 Baseline Characteristics A total of 200 elderly male patients with type 2 diabetes who underwent CGM were included. Baseline characteristics are presented in Table 1 . The TIR<85% group had significantly higher age, diabetes duration, FPG, 2hPG, baseline HbA1c, MAGE, CV, and insulin therapy proportion compared to the TIR$ $85% group (all $P<0.05$), while BMI was significantly lower ($P<0.05$).

2.2 Differences in Long-term Glycemic Variability by TIR Level Differences in HbA1c variability during long-term follow-up by TIR level are shown in Table 2 . The mean annual number of HbA1c measurements did not differ significantly between groups. However, the TIR<85% group exhibited significantly higher mean HbA1c ($7.44\$\pm0.63\pm0.76\pm3.82\pm4.45\pm20.4 vs. 32.5\pm20.9$) $compared to the TIR$ $85% group (all $P<0.05$).

2.3 Univariate Correlation Analysis Between TIR and Long-term Glycemic Variability Univariate Pearson correlation analysis revealed that TIR was significantly correlated with mean HbA1c ($r=-0.395$, $P<0.001$), HbA1c CV ($r=-0.239$, $P<0.001$), and HVS ($r=-0.400$, $P<0.001$).

2.4 Univariate Linear Regression Analysis of TIR and Long-term Glycemic Variability Univariate linear regression analysis with TIR as the independent variable and mean HbA1c, HbA1c CV, or HVS as dependent variables showed significant associations between TIR and mean HbA1c (β=-0.02,

95%CI -0.03~-0.01, P<0.001, R^2=0.156), HbA1c CV (β=-0.06, 95%CI -0.10~-0.03, P=0.001, R^2=0.057), and HVS (β=-0.55, 95%CI -0.72~-0.37, P<0.001, R^2=0.160) (Table 3).

2.5 Multivariate Linear Regression Analysis of TIR and Long-term Glycemic Variability Multivariate linear regression analyses were performed with mean HbA1c, HbA1c CV, or HVS as dependent variables and TIR, age, BMI, diabetes duration, FPG, MAGE, and insulin therapy (1=yes, 0=no) as independent variables. As shown in Table 3 , after adjusting for relevant confounders, TIR remained independently associated with mean HbA1c (β=-0.01, 95%CI -0.02~0.00, P=0.002, R^2=0.329), HbA1c CV (β=-0.07, 95%CI -0.12~-0.03, P=0.003, R^2=0.100), and HVS (β=-0.44, 95%CI -0.67~-0.21, P<0.001, R^2=0.234).

Discussion

This study demonstrates that TIR is independently associated with HbA1c variability during long-term follow-up in elderly male patients with type 2 diabetes, with lower TIR values indicating more pronounced long-term glycemic variability. These findings provide additional evidence for using TIR as a glycemic management metric in elderly patients with type 2 diabetes.

Current research has established close relationships between TIR and diabetic complications. TIR correlates with the prevalence and severity of diabetic retinopathy, with lower TIR and greater glycemic variability associated with more severe retinopathy. El Malahi et al. found that TIR was associated with microvascular complications in type 1 diabetes, whereas glycemic variability was not. Lu et al. followed patients with type 2 diabetes for an average of 6.9 years and reported that 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 have recommended TIR as a primary metric in CGM reports and for glycemic management in diabetes patients.

TIR is closely related to other glycemic metrics. Vigersky and McMahon reviewed 18 randomized controlled trials and found a linear relationship between TIR and HbA1c in patients with diabetes (R=-0.84, R^2=0.71). Beck et al. conducted a pooled analysis of four randomized studies and found that TIR was significantly associated with mean glucose and moderately correlated with HbA1c in type 1 diabetes. Research has also demonstrated strong relationships between TIR and short-term glycemic variability indices such as MAGE and CV. However, studies examining the relationship between TIR and long-term glycemic variability are lacking. In our cohort with relatively stable glycemic control, we used TIR>85% as the cutoff for optimal control based on previous research. Our results demonstrate linear relationships between TIR and both HbA1c CV

and HVS during long-term follow-up, with HbA1c CV and HVS increasing progressively as TIR decreased, indicating more pronounced long-term glycemic variability.

Long-term glycemic variability, reflecting glucose fluctuations over months to years, is primarily manifested as HbA1c variability during follow-up. Most studies have used HbA1c CV and standard deviation to assess long-term glycemic variability. Mao et al. found that HbA1c CV was an independent risk factor for microvascular complications in type 1 diabetes. An observational study using HbA1c standard deviation and CV to evaluate long-term glycemic variability reported associations between HbA1c variability and increased risks of all-cause mortality, cardiovascular death, and diabetic complications. However, HbA1c standard deviation and CV are not easily interpretable in clinical practice. In recent years, HVS has been proposed as an alternative measure, representing the proportion of adjacent HbA1c measurements that differ by $ $0.5%. Li et al. found that HVS was independently associated with increased risks of all-cause mortality, cardiovascular events, and microvascular complications in newly diagnosed type 2 diabetes. Mao et al. reported that combined HVS and obesity were associated with increased risks of all-site cancer and cancer-related mortality in 15,286 patients with diabetes.

Current guidelines recommend TIR as a novel and useful glycemic management metric, though HbA1c remains the primary indicator of glycemic control. Nevertheless, HbA1c has certain limitations. Our study demonstrates that TIR is significantly associated with mean HbA1c during long-term follow-up and can reflect long-term glycemic variability, supporting TIR as an effective complement to HbA1c. CGM provides comprehensive and reliable glucose information through continuous monitoring of interstitial fluid glucose concentrations. While CGM-derived metrics such as MAGE and CV are widely used in clinical and research settings to quantify glycemic fluctuations, they are difficult for patients to understand. TIR is simple, intuitive, and easily understood, and our findings show it is not only related to short-term glycemic control but also effectively reflects long-term glycemic variability, helping clinicians predict future glycemic fluctuations and facilitating self-management in elderly patients with type 2 diabetes.

This study has several limitations. The cohort consisted of elderly men with relatively stable glycemic control, and the sample size was small, making this a preliminary exploratory study that requires confirmation through multicenter, large-sample prospective studies. In summary, our analysis of elderly male patients with type 2 diabetes who underwent CGM demonstrates that TIR is associated with long-term glycemic variability, with lower TIR values indicating more pronounced HbA1c variability. During the management of elderly patients with type 2 diabetes, TIR may help predict future glycemic variability and contribute to long-term glycemic management.

Author Contributions

FANG Fu-sheng conceptualized the study, designed the research protocol, performed statistical analysis, drafted the manuscript, and interpreted the results. WANG Ning, LIU Xing-yu, and YAN Shuang-tong conducted the research, collected data, and performed literature searches. LI Chun-lin 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 conflicts of interest.

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