Correlation Between Glycemic Variability and Cognitive Function in Patients with Type 2 Diabetes Mellitus and Recent Small Subcortical Infarcts: A Postprint

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Abstract

Background Recent small subcortical infarction (RSSI) is a manifestation of lacunar cerebral infarction, a common brain disease that can lead many patients to clinical outcomes of disability or dementia. However, the relationship between infarct burden and cognitive function and blood glucose fluctuations in patients with type 2 diabetes mellitus (T2DM) complicated by recent small subcortical infarction is not entirely clear. Objective To explore the correlation between glycemic variability (GV) and infarct burden and cognitive function in patients with type 2 diabetes mellitus complicated by recent small subcortical infarction, and to construct a risk prediction model. Methods Clinical basic data of 140 patients with RSSI complicated by T2DM were recorded and 72-hour continuous glucose monitoring was performed. Infarct burden was evaluated using magnetic resonance imaging manifestations; cognitive function was assessed using the Montreal Cognitive Assessment (MoCA). Multivariate Logistic regression analysis was used to investigate the influencing factors of infarct burden and cognitive impairment in patients with RSSI complicated by T2DM, and based on the results, receiver operating characteristic curve (ROC) was plotted to evaluate the predictive value of glycemic variability for cognitive impairment in patients with type 2 diabetes mellitus complicated by recent small subcortical infarction, and a nomogram prediction model was constructed and its predictive value was analyzed. Results There were significant differences in standard deviation of mean blood glucose concentration (SD), percentage coefficient of variation (%CV), and time in range (TIR) between low and high burden groups (P<0.05). There were significant differences in SD, %CV, and TIR between groups with and without cognitive impairment (P<0.05). Logistic regression analysis showed that elevated SD (OR=4.201, 95%CI (1.380,12.788), P=0.011)

and %CV [OR=1.218, 95%CI (1.096,1.354), P<0.01] were risk factors for increased infarct burden in patients with RSSI complicated by T2DM; elevated TIR [OR= 0.866, 95%CI (0.814,0.921), P<0,01] was a protective factor. Elevated SD [OR=2.947, 95%CI (1.150,7.548), P=0.024] and %CV [OR=1.174, 95%CI (1.072,1.287), P=0.001] were risk factors for cognitive impairment in patients with RSSI complicated by T2DM; elevated TIR [OR= 0.954, 95%CI (0.917,0.992), P=0.018] was a protective factor. A nomogram prediction model for the risk of cognitive impairment in patients with RSSI complicated by T2DM was established based on SD, %CV, and TIR. Decision curve analysis (DCA) was used for internal validation of clinical benefit, and the results suggested that the prediction model had substantial clinical benefit. Internal calibration was also performed, indicating that the actual prediction results were close to the ideal prediction results. ROC curves of SD, %CV, and TIR for predicting cognitive impairment in patients with RSSI complicated by T2DM were plotted, and the results showed that %CV and TIR had greater predictive value. The area under the curve (AUC) of %CV and TIR for predicting cognitive impairment in patients with type 2 diabetes mellitus complicated by recent small subcortical infarction were %CV: AUC 0.758 [95%CI (0.66,0.856), P<0.01], TIR: AUC 0.714 [95%CI (0.624,0.804), P<0.01]. Conclusion Glycemic variability is closely related to the degree of infarct burden in patients with type 2 diabetes mellitus complicated by recent small subcortical infarction, and is closely related to the occurrence of cognitive dysfunction in patients with type 2 diabetes mellitus complicated by recent small subcortical infarction. Among them, %CV and TIR have good predictive value for cognitive dysfunction in patients with type 2 diabetes mellitus complicated by recent small subcortical infarction. Improving the degree of blood glucose fluctuation may have certain clinical value in preventing the occurrence of recent small subcortical infarction and preventing the occurrence of cognitive impairment.

Full Text

Correlation between Blood Glucose Variability and Cognitive Function in Patients with Type 2 Diabetes Mellitus Complicated with Recent Small Subcortical Infarction

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Abstract

Background: Recent small subcortical infarction (RSSI) represents a manifestation of lacunar infarction and is a common cerebrovascular condition that

often leads to disability or dementia. However, the relationship between infarct burden, cognitive function, and blood glucose fluctuations in patients with type 2 diabetes mellitus (T2DM) complicated with RSSI remains unclear.

Objective: To investigate the correlation between glucose variability (GV) and infarct burden as well as cognitive function in T2DM patients with RSSI, and to construct a risk prediction model.

Methods: Clinical data from 140 RSSI patients with T2DM were collected, and 72-hour continuous glucose monitoring was performed. Infarct burden was evaluated using magnetic resonance imaging, while cognitive function was assessed with the Montreal Cognitive Assessment (MoCA) scale. Multivariate logistic regression analysis was employed to identify factors influencing infarct burden and cognitive impairment. Receiver operating characteristic (ROC) curves were constructed to evaluate the predictive value of GV for cognitive impairment in T2DM patients with RSSI. A nomogram prediction model was developed and its predictive value was analyzed.

Results: Significant differences were observed between low and high infarct burden groups in standard deviation of glucose (SD), coefficient of variation percentage (%CV), and time in range (TIR) ($P<0.05$). Similarly, SD, %CV, and TIR differed significantly between patients with and without cognitive impairment ($P<0.05$). Logistic regression analysis revealed that elevated SD [OR=4.201, 95%CI (1.380,12.788), P=0.011] and %CV [OR=1.218, 95%CI (1.096,1.354), $P<0.01$] were risk factors for increased infarct burden, while elevated TIR [OR=0.866, 95%CI (0.814,0.921), $P<0.01$] was protective. For cognitive impairment, elevated SD [OR=2.947, 95%CI (1.150,7.548), P=0.024] and %CV [OR=1.174, 95%CI (1.072,1.287), P=0.001] were risk factors, whereas elevated TIR [OR=0.954, 95%CI (0.917,0.992), P=0.018] was protective. A nomogram prediction model for cognitive impairment risk was established based on SD, %CV, and TIR. Decision curve analysis (DCA) demonstrated substantial clinical benefit, and internal calibration showed close agreement between predicted and actual outcomes. ROC analysis indicated that %CV and TIR had good predictive value, with AUCs of 0.758 [95%CI (0.66,0.856), $P<0.01$] and 0.714 [95%CI (0.624,0.804), $P<0.01$], respectively.

Conclusion: Glucose variability is closely associated with infarct burden and cognitive dysfunction in T2DM patients with RSSI. %CV and TIR demonstrate good predictive value for cognitive impairment in this population. Clinical monitoring and improvement of GV may help prevent RSSI occurrence and cognitive decline.

Keywords: glucose variability; recent small subcortical infarction; cerebral small vessel disease; type 2 diabetes mellitus; time in range; nomogram

Introduction

Stroke is the second leading cause of death worldwide and a major cause of disability. Ischemic stroke comprises several subtypes, including large artery atherosclerosis, cardioembolism, and cerebral small vessel disease (cSVD). Among these, lacunar infarction (LI) is the most typical manifestation of cSVD, accounting for 20-30% of all ischemic strokes. Lacunar infarction includes both recent small subcortical infarcts (RSSI) and lacunes. RSSI is defined on neuroimaging as a recently occurred small infarction in the distribution area of perforating arteries, appearing as hypointense on T1WI, hyperintense on T2WI and FLAIR sequences, with an axial diameter <20 mm and coronal or sagittal diameter >20 mm, and hyperintense on DWI. Despite their small size, RSSI lesions can lead to significant disability or dementia, warranting particular attention due to their 20% recurrence rate, 25% five-year mortality, and association with vascular cognitive impairment.

Type 2 diabetes mellitus (T2DM) is a common condition in elderly populations. While glycated hemoglobin (HbA1c) measurement remains the gold standard for assessing glycemic control, it does not capture fluctuations in blood glucose levels, known as glucose variability (GV). GV represents fluctuations in glucose levels throughout the day and across different days, including episodes of hyperglycemia and hypoglycemia. Advances in continuous glucose monitoring (CGM) technology have made GV assessment readily available, providing deeper insights into daily glucose fluctuations. Key GV metrics include the standard deviation of mean glucose concentration (SD), coefficient of variation percentage (%CV), largest amplitude of glucose excursion (LAGE), and the emerging metric time in range (TIR), which measures the percentage of time glucose remains within target range.

Both RSSI and T2DM are prevalent conditions. Recent studies have demonstrated that GV affects cognitive function in elderly T2DM patients, and previous research has shown that glucose fluctuations influence small artery pathology. These findings suggest a potential link between GV and infarct burden as well as cognitive dysfunction in T2DM patients with RSSI. However, the relationship between GV and infarct severity or cognitive impairment in this specific population remains poorly understood. Clarifying this relationship could facilitate identification of high-risk individuals and assessment of disease severity and prognosis. Therefore, this study aimed to investigate the correlation between GV and infarct burden as well as cognitive function in T2DM patients with RSSI, and to develop a clinically meaningful risk prediction model to identify specific, sensitive, and easily measurable early diagnostic indicators for cognitive dysfunction in this population, enabling clinicians to formulate effective prevention and treatment strategies.

1.1 General Data Collection

We retrospectively screened 140 patients with T2DM complicated by RSSI who were admitted to the Second Affiliated Hospital of Zhengzhou University between January 2021 and June 2022. Based on imaging findings, patients were divided into a high infarct burden group (>1 infarct lesion, n=45) and a low burden group (single lesion, n=95). According to the presence of cognitive dysfunction, they were further categorized into a cognitive impairment group (n=36) and a normal cognition group (n=104).

Inclusion criteria were: (1) diagnosis of T2DM according to the "Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes Mellitus (2017 Edition)" ; (2) diagnosis of RSSI based on the "Chinese Expert Consensus on the Diagnosis and Treatment of Cerebral Small Vessel Disease 2021"; (3) completion of routine blood tests and 72-hour glucose monitoring during hospitalization; (4) completion of brain magnetic resonance imaging; and (5) age >18 years. Exclusion criteria included: (1) other intracranial conditions such as infection, large-area cerebral infarction, hemorrhage, tumor, or trauma; (2) incomplete clinical baseline data; (3) severe infectious or immune diseases; (4) important organ structural or functional damage; and (5) lack of informed consent. This study was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Zhengzhou University (Approval No.: 2022031).

For all enrolled patients, we recorded: Montreal Cognitive Assessment (MoCA) scores, body mass index (BMI), history of hypertension and coronary artery disease, age, sex, fasting blood glucose, lipid profile, homocysteine (Hcy), glycosylated hemoglobin (HbA1c), C-reactive protein (CRP), smoking history (accumulated >12 months, >5 cigarettes/day), and alcohol consumption history (alcohol intake >50 g/day, accumulated >6 months).

1.2 Assessment of Glucose Variability

After admission, patients underwent 72-hour continuous glucose monitoring (CGM). GV assessment indicators were calculated, including: standard deviation of glucose (SD), coefficient of variation percentage (%CV), largest amplitude of glucose excursion (LAGE), and time in range (TIR). %CV was calculated as (glucose SD/mean glucose) × 100%; LAGE was defined as the difference between maximum and minimum glucose values; TIR was defined as the percentage of time during the 72-hour period that glucose remained within the target range of 3.9-7.8 mmol/L.

1.3 Assessment of Infarct Burden

All patients underwent brain magnetic resonance imaging. RSSI was defined as described above. Based on the number of infarct lesions, patients were classified into high burden (>1 lesion) and low burden (single lesion) groups. Imaging evaluation was performed by two neurologists, with discrepancies resolved through consultation.

1.4 Assessment of Cognitive Function

All patients completed the Montreal Cognitive Assessment (MoCA). A total score $ $26 was defined as cognitive impairment.

1.5 Statistical Methods

Statistical analysis was performed using SPSS 26.0 software. Normally distributed continuous variables were expressed as mean ± standard deviation and compared between groups using t-tests. Non-normally distributed continuous variables were expressed as median (P25, P75) and compared using Mann-Whitney U tests. Categorical variables were analyzed using ^{2} tests. Multivariate logistic regression analysis was used to explore factors influencing infarct burden and cognitive function in RSSI patients with T2DM. Using R software (version 4.2.1), a nomogram prediction model for cognitive impairment risk was constructed based on GV indicators. Internal calibration analysis was performed, and clinical benefit was validated using decision curve analysis (DCA). ROC curves were plotted to evaluate the predictive value of GV indicators for cognitive impairment in RSSI patients with T2DM. $P<0.05$ was considered statistically significant.

Results

2.1 Comparison of Clinical Indicators Between Groups

No significant differences were found between low and high infarct burden groups in terms of hypertension history, coronary artery disease history, age, lipid profile, smoking history, alcohol consumption history, fasting blood glucose, Hcy, CRP, or BMI ($P>0.05$). However, GV-related indicators showed significant differences: SD and %CV were higher in the high burden group, while TIR was lower ($P<0.05$) . Similarly, comparison of GV indicators between cognitive function groups revealed that SD and %CV were higher in the cognitive impairment group, while TIR was lower ($P<0.05$) .

2.2 Multivariate Logistic Regression Analysis

Using infarct burden and cognitive impairment as dependent variables (assigned as 1=yes, 0=no), and SD, %CV, and TIR as independent variables (using actual measured values), multivariate logistic regression analysis showed that elevated SD [OR=4.201, 95%CI (1.380,12.788), P=0.011] and %CV [OR=1.218, 95%CI (1.096,1.354), $P<0.01$] were independent risk factors for high infarct burden, while elevated TIR [OR=0.866, 95%CI (0.814,0.921), $P<0.01$] was protective. For cognitive impairment, elevated SD [OR=2.947, 95%CI (1.150,7.548), P=0.024] and %CV [OR=1.174, 95%CI (1.072,1.287), P=0.001] were risk factors, whereas elevated TIR [OR=0.954, 95%CI (0.917,0.992), P=0.018] was protective [TABLE:3, TABLE:4].

2.3 Predictive Value of GV Indicators for Cognitive Impairment

ROC curves based on SD, %CV, and TIR for predicting cognitive impairment showed that SD had an AUC of 0.680 [95%CI (0.574,0.786), P=0.001] with an optimal cutoff of 3.100, sensitivity of 58.3%, and specificity of 77.9%. %CV demonstrated an AUC of 0.758 [95%CI (0.66,0.856), P<0.01] with an optimal cutoff of 29.485, sensitivity of 66.7%, and specificity of 76.0%. TIR showed an AUC of 0.714 [95%CI (0.624,0.804), P<0.01] with an optimal cutoff of 60.5, sensitivity of 97.2%, and specificity of 44.2%. These results indicate that %CV and TIR have good predictive value for cognitive impairment in RSSI patients with T2DM [Figure 1: see original paper].

2.4 Development and Clinical Validation of a Nomogram Prediction Model

A nomogram prediction model for cognitive impairment risk in RSSI patients with T2DM was developed based on SD, %CV, and TIR [Figure 2: see original paper]. DCA validation demonstrated substantial clinical benefit, indicating good clinical predictive value [Figure 3: see original paper]. Internal calibration showed close agreement between predicted and actual outcomes [Figure 4: see original paper].

Discussion

Previous studies have identified multiple factors associated with RSSI severity, though the exact mechanisms remain unclear. The primary pathophysiological mechanisms are believed to involve endothelial dysfunction and blood-brain barrier disruption. RSSI likely results from cerebral atherosclerosis and endothelial dysfunction, with local thrombus formation on atherosclerotic plaques that propagates along perforating arteries and progressive occlusion of collateral vessels. Endothelial dysfunction may be the most critical factor, as the endothelium regulates vascular tone, participates in inflammatory responses, and contributes to vascular wall formation. Its dysfunction promotes vasoconstriction, procoagulation, inflammation, and increased vascular thickness, leading to structural and functional vascular damage, increased vascular permeability, impaired autoregulation, reduced perfusion, and eventual luminal narrowing, thrombosis, and occlusion.

GV refers to fluctuations in blood glucose levels throughout the day and across different days, including hyperglycemic and hypoglycemic episodes. TIR serves as a convenient, intuitive, and easily measurable indicator that can predict the risk of long-term diabetic complications. Various studies worldwide have attributed diabetic complications to hyperglycemia, glucose abnormalities, and glucose level fluctuations. Previous research has demonstrated associations between GV and arterial stiffness, as well as positive correlations between GV and ischemic stroke risk. These findings suggest that glucose fluctuations may influence the pathological progression of RSSI. Additionally, studies have confirmed

that T2DM patients with greater GV exhibit more pronounced cognitive decline, indicating that GV may impact cognitive function in RSSI patients with T2DM.

Our results demonstrate that GV is a risk factor for increased infarct burden and cognitive impairment in RSSI patients with T2DM. This suggests that assessing GV at admission may help identify patients at risk for increased infarct burden and cognitive dysfunction, enabling early intervention to prevent RSSI occurrence and progression, reduce severity, improve prognosis, and prevent cognitive damage. Achieving individualized glucose homeostasis through GV modulation may have important clinical implications for reducing overall diabetes-related complications.

The mechanisms through which GV affects cognitive function may involve damage to brain cells in cognitive regions such as the hippocampus, cerebellum, and frontal lobe. Subcortical infarcts resulting from GV disrupt network connections between subcortical structures and the prefrontal, frontal, and cingulate cortices, inhibiting cognitive-related functions in the frontal cortex. Additionally, cerebrovascular structural damage leads to impaired cerebral autoregulation and may contribute to amyloid angiopathy, progressively reducing cognitive function and causing cognitive impairment.

Compared with previous studies, our use of SD, %CV, LAGE, and TIR provides a more comprehensive and effective description of GV. Statistical analysis confirmed the close relationship between GV and both infarct burden and cognitive function in RSSI patients with T2DM. The nomogram prediction model we developed offers a concise and intuitive tool for reflecting the relationship between cognitive impairment risk and various risk factors.

This study has several limitations. First, it is a retrospective, single-center study with a relatively small sample size, which may introduce selection bias. Second, GV indicators were calculated primarily from single admission blood tests, which may have lower accuracy and potential systematic errors. Finally, the prediction model was only internally validated and lacks external validation.

In conclusion, GV is closely associated with infarct burden and cognitive impairment in T2DM patients with RSSI. Early assessment of GV indicators in these patients can improve early identification of infarct severity and prognosis. GV modification may represent a potential approach for preventing RSSI occurrence and progression, and monitoring changes in %CV and TIR may help predict cognitive dysfunction development. Enhanced management of these risk factors may slow infarct progression, reduce severity, and improve prognosis.

Author Contributions: Meng Qizhe conceived the study objectives and designed the research protocol and model. Yang Xiaopeng conducted feasibility analysis and provided oversight. Wang Ming and Wang Yang collected clinical data. Meng Qizhe and Wang Yang performed statistical analysis. Meng Qizhe and Xi Zhi drafted the manuscript. Yang Xiaopeng reviewed, revised, and quality-controlled the final manuscript. All authors approved the final version.

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