ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2023 February 16; 11(5): 979-1223

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

Contents

Thrice Monthly Volume 11 Number 5 February 16, 2023

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Study

Observational Study

CASE REPORT

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 5 February 16, 2023

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 5 February 16, 2023

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 5 February 16, 2023

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Tian-Biao Zhou, MD, PhD, Chief Doctor, Professor, Department of Nephrology, Second Affiliated Hospital, Shantou University Medical College, Shantou 515041, Guangdong Province, China. zhoutb@aliyun.com

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Current Contents®/Clinical Medicine, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJCC* as 1.534; IF without journal self cites: 1.491; 5-year IF: 1.599; Journal Citation Indicator: 0.28; Ranking: 135 among 172 journals in medicine, general and internal; and Quartile category: Q4. The *WJCC*'s CiteScore for 2021 is 1.2 and Scopus CiteScore rank 2021: General Medicine is 443/826.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

PUBLICATION DATE
February 16, 2023

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 February 16; 11(5): 1019-1030

DOI: 10.12998/wjcc.v11.i5.1019

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Study

Relationship between glycemic variability and cognitive function in lacune patients with type 2 diabetes

Qi-Zhe Meng, Yang Wang, Bing Li, Zhi Xi, Ming Wang, Jia-Qi Xiu, Xiao-Peng Yang

Specialty type: Clinical neurology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Byeon H, South Korea; Pandey NM, India

Received: November 7, 2022
Peer-review started: November 7, 2022
First decision: December 20, 2022
Revised: December 26, 2022
Accepted: January 10, 2023
Article in press: January 10, 2023
Published online: February 16, 2023

Qi-Zhe Meng, Yang Wang, Bing Li, Zhi Xi, Ming Wang, Jia-Qi Xiu, Xiao-Peng Yang, Department of Neurology, The Second Affiliated Hospital of Zhengzhou University, Zhengzhou 450003, Henan Province, China

Corresponding author: Xiao-Peng Yang, Doctor, Chief Doctor, Department of Neurology, The Second Affiliated Hospital of Zhengzhou University, Jingba Road, Jinshui District, Zhengzhou 450003, Henan Province, China. yaxipe39@126.com

Abstract

BACKGROUND

Lacunes are the manifestations of lacunar infarction which can lead many patients to the clinical outcome of disability or dementia. However, the relationship between lacune burden, cognitive function and blood glucose fluctuation in patients with type 2 diabetes mellitus (T2DM) complicated with lacunes is not very clear.

AIM

To explore the correlation between glucose variability, lacune burden and cognitive function in patients with lacunes complicated with T2DM.

METHODS

The clinical and imaging data of 144 patients with lacunes combined with T2DM were reviewed retrospectively. 72 h continuous glucose monitoring was performed. The Montreal Cognitive Assessment was used to assess cognitive function. The burden of lacunes was evaluated using magnetic resonance imaging performance. Multifactorial logistic regression analysis was used to study the affecting the lacune load and cognitive impairment in patients. To predict the value of patients' cognitive impairment with lacunes complicated with T2DM, a receiver operating characteristic (ROC) curve and a nomogram prediction model were constructed.

RESULTS

The standard deviation (SD) of the average blood glucose concentration, percentage coefficient of variation (%CV) and time of range (TIR) were significantly different between the low and the high load groups ($P < 0.05$). The SD, %CV and TIR of the cognitive impairment group and non-cognitive impairment group were significantly different ($P < 0.05$). SD (odds ratio (OR): 3.558, 95% confidence interval (CI): 1.268-9.978, $P = 0.006$), and %CV (OR: 1.192,

95%CI: 1.081-1.315, $P < 0.05$) were the risk factors for an increased infarct burden in lacunes patients complicated with T2DM. TIR (OR: 0.874, 95%CI: 0.833-0.928, $P < 0.05$) is a protective factor. In addition, an increased SD (OR: 2.506, 95%CI: 1.008-6.23, $P = 0.003$), %CV (OR: 1.163, 95%CI: 1.065-1.270, $P < 0.05$) were the risk factors for cognitive impairment in patients with lacunes complicated with T2DM, TIR (OR: 0.957, 95%CI: 0.922-0.994, $P < 0.05$) is a protective factor. A nomogram prediction model of the risk of cognitive impairment was established based on SD, %CV and TIR. Decision curve analysis and the internal calibration analysis were used for internal verification and showed that the model was clinical benefit. The area under the ROC curves for predicting cognitive impairment in patients with lacunes complicated with T2DM was drawn were %CV: 0.757 (95%CI :0.669-0.845, $P < 0.05$), TIR: 0.711 (95%CI: 0.623-0.799, $P < 0.05$).

CONCLUSION

Blood glucose variability is closely associated with the level of lacune burden and cognitive dysfunction in lacune patients combined with T2DM. %CV, TIR have a certain predictive effect in cognitive impairment in lacune patients.

Key Words: Blood glucose variability; Lacunes; Type 2 diabetes; Cognitive impairment; Nomograms

Core Tip: Standard deviation, percentage of coefficient of variation, largest amplitude of glucose, and time of range were used in this study describe the degree of glucose variability (GV) more comprehensively and effectively in patients. Statistical analysis confirmed the close relationship between GV, lacune burden and cognitive function in lacune patients with type 2 diabetes mellitus (T2DM). In addition, a nomogram prediction model of GV index and lacunes complicated with T2DM patients with cognitive impairment was established, which could concisely and intuitively reflect the relationship between the risk of cognitive impairment in lacune patients complicated with T2DM and various risk factors.

Citation: Meng QZ, Wang Y, Li B, Xi Z, Wang M, Xiu JQ, Yang XP. Relationship between glycemic variability and cognitive function in lacune patients with type 2 diabetes. *World J Clin Cases* 2023; 11(5): 1019-1030
URL: https://www.wjgnet.com/2307-8960/full/v11/i5/1019.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i5.1019

INTRODUCTION

Cerebral infarction is the major reason of the disability and the second major cause of death worldwide [1]. Ischemic stroke has different subtypes including cerebral small vessel disease (CSVD), aortic atherosclerosis and cardiac embolism. Although CSVD has many imaging and clinical characteristics, cavitary infarction (LI) is the most typical accounting for 20%-30% of ischemic stroke cases[2]. LI encompasses recent small subcortical infarcts and lacunes. Lacunes are the most common imaging findings of LI[3]. Lacune is defined as a lumen filled with a circular or elliptical subcortical space 3-15 diameter and is consistent with previous acute subcortical infarction in the perforated arteriole area[4]. Lacunes represent large problems that can drive patients toward a clinical outcome of disability or dementia. Lacune requires special attention because it has a recurrence rate of 20%, a 5-year mortality rate of 25%, and related diseases such as vascular cognitive impairment[5]. T2DM is a common disease in older adults; although determination of glycated hemoglobin (HbA1c) is considered to be the standard for evaluation of glycemic control in diabetic patients, it does not consider changes in blood glucose levels, that is, blood glucose variability (GV)[6]. GV, the cause of glycemic fluctuations, is a sensitive indicator of blood sugar, and advances in continuous blood glucose monitoring (CGM) technology have become an established evaluation tool[7]. CGM technology can further understand daily fluctuations and changes in the daily glucose concentration. The measurement of blood GV includes the standard deviation (SD) of the average blood glucose concentration, the percentage of coefficient of variation (%CV), the largest amplitude of glucose (LAGE), and the determination of the time within the blood glucose range, a newly discovered indicator in recent years, as the result of blood glucose control. Lacunes and type 2 diabetes (T2DM) are both common diseases in the population. Recently, it is clarified that the degree of GV will affect the cognitive function of elderly T2DM patients[8]. In previous studies, changes in blood glucose also affected pathological changes in small arterioles[9]. This indicates that the blood glucose level in lacune patients with T2DM may be closely associate with infarction load and cognitive dysfunction. However, the association between GV, the severity of lacunes and the

cognitive impairment in lacune patients with T2DM is still unknown. If we can understand the correlation between GV and cognitive function in lacune patients combined with T2DM, we can easily identify high-risk groups, and judge the severity and prognosis of the disease.

The purpose of this research was to investigate the association between GV, lacune burden and cognitive function in patients with lacunes complicated with T2DM, and to find out the relevant factors for cognitive dysfunction in lacune patients with T2DM. Specificity, sensitivity, and indicators for early clinical diagnosis will allow clinicians to formulate effective preventive strategies and treatment measures as soon as possible.

MATERIALS AND METHODS

Study population

PASS11 was used to estimate the sample size ($\alpha = 0.05$, $\beta = 0.1$, two-sided test, balanced group design). Based on the assumption of homogeneity of variances, pooled variance was used to calculate the sample size. According to previous literature reports and preliminary experiments, substituting the test level, test efficiency, mean and standard deviation of the experimental group and the control group, we calculated that at least 120 patients need to be enrolled. Considering the loss of follow-up of the subjects, at least 140 patients need to be included. In total, 144 patients with lacunes combined with T2DM treated at the second hospital of Zhengzhou University from January 2021 to June 2022 were retrospectively screened (Figure 1). According to the appearance of lacunes on imaging, patients were divided into the high-load group (lacune lesions > 3, $n = 50$) and low load group (lacune lesions 1-3, $n = 94$)[10]. Cognitive function disorder ($n = 37$) and normal cognitive function ($n = 107$) patients were classified according to whether or not cognitive dysfunction occurred. The inclusion criteria were as follows: (1) Patients compatible with T2DM diagnostics criteria established by the 'China Diabetes Prevention and Treatment Guideline (2017 Edition)"[11]; (2) patients who met the "Diagnostic Criteria of Lacunes" in the 2021 "Chinese Common Cerebrovascular Disease Medical Specialist Common Recognition" guidelines[12]; (3) routine blood tests performed on admission, and baseline data such as blood lipids and blood sugar levels were complete; and (4) head magnetic resonance imaging (MRI) was recorded on admission. The exclusion criteria were as follows: (1) Other intracranial diseases such as intracranial infection, massive cerebral infarction, cerebral hemorrhage, and tumor, trauma; (2) taking medications that may affect cognitive function; (3) combined with severe infectious and metabolic diseases; (4) combined with structural or functional damage of vital organs; (5) age < 18 years; and (6) no informed consent was signed. This study was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Zhengzhou University (2022031).

Data collection

The following data was collected from all patients who participated in this study: Montreal cognitive assessment (MoCA) score, body mass index (BMI), history of hypertension, history of coronary heart disease, age, gender, fasting blood glucose, blood lipids, homocysteine (Hcy), HbA1c, C-reactive protein (CRP), smoking history (more than 12 mo in total, > 3 cigarettes/d) and drinking history (intake of alcohol content > 50 g/d, > 6 mo in total).

GV assessment

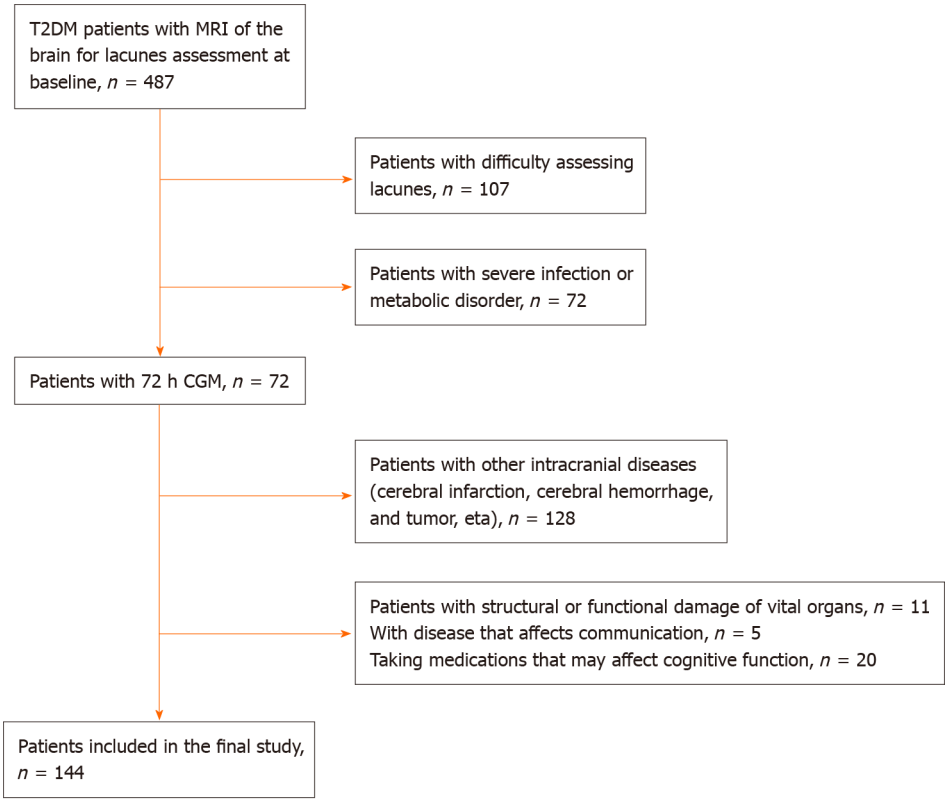
Patients underwent CGM (Abbott Diabetes Care Inc, England) for 72 h after admission, and GV evaluation indicators were calculated, which included: standard deviation (SD) of the mean blood glucose concentration, %CV, LAGE and glucose target range time (TIR). The %CV = SD/mean blood sugar × 100%; LAGE = the maximum minus minimum blood glucose, and the glucose TIR was defined as the percentage time that glucose was in the target range (3.9-7.8 mmol/L) within 72 h.

Lacune evaluation

All selected patients completed an MRI of the head. In this study, the number of lacunes is used to evaluate the infarct burden of lacunes. Lacune was defined as a cavity that appeared on MRI as a subcortical, round or oval, fluid-filled cavity resembling a cerebrospinal fluid signal that was low on T1-weigthed imaging (WI) sequences, high on T2WI sequences, and low in the center surrounded by a high signal ring on fluid-attenuated inversion recover sequences; the diameter was 3-15 mm. Patients were divided into a high-load group (lacunes > 3) and a low-load group (lacunes: 1-3) according to the number of lacunes,. Evaluations were performed by two neurologists, and in the event of disagreement, both were consulted.

Cognitive function assessment

All enrolled patients completed the MoCA. A total score < 26 was defined as a patient with cognitive impairment, whereas a score of 26 and above was defined as normal.



DOI: 10.12998/wjcc.v11.i5.1019

Figure 1 Flowchart of enrollment of study patients. T2DM: Type 2 diabetes mellitus; MRI: Magnetic resonance imaging; CGM: Continuous blood glucose monitoring.

Statistical analysis

SPSS (v.26.0) software was used for statistical analysis. The measurement data that conformed to the normal distribution was expressed as the mean ± standard deviation (mean ± SD) and a comparison between the two groups was made using the Student's *t*-test. The measurement data that was not normally distributed was expressed as the median with the 25th and 75th percentiles (M; P25, P75); the Mann-Whitney U test was used for comparison between the two groups. The χ^2 test was used for the analysis of enumeration data. Multivariate Logistic regression analysis was used to explore the influencing factors of lacune burden and cognitive function in patients with lacunes complicated with T2DM. Using the R 4.2.1 software package, a nomogram prediction model of blood GV indicators for cognitive impairment in patients with lacunes complicated with T2DM was established. The internal correction analysis was used, and the clinical benefit was verified with decision curve analysis (DCA). A receiver operating characteristic (ROC) curve was used curve to evaluate the predictive value of each index on cognitive function in patients with lacunes complicated with T2DM. $P < 0.05$ was statistically significant.

RESULTS

Comparison of clinical indices

In patients with lacunes, the low-load groups and high-load groups showed no significant difference in BMI, hypertension history, coronary sclerosis history, age, lipid levels, smoking history, drinking history, fasting blood sugar, and CRP (all $P > 0.05$). Among the GV-related indicators, SD and %CV in the high-load group were higher than those in the low load group, whereas TIR was lower in the high-load; and the differences were statistically significant ($P < 0.05$; Table 1). The GV indexes of the two groups of patients defined by cognitive impairment were compared. The SD and %CV of the cognitive impairment group were higher than those of the normal cognitive group, whereas the TIR was lower in the cognitive impairment group; the differences were statistically significant ($P < 0.05$; Table 2). Multivariate logistic regression analysis was performed for lacune complicated with T2DM patients with lacune load and degree of cognitive impairment as dependent variables, and SD, %CV, and TIR as independent variables. Elevated SD and %CV were the risk factors of a high lacune burden and cognitive impairment in lacune patients complicated with T2DM ($P < 0.05$). In addition, elevated

Table 1 Comparison of clinical data regarding lacune burden

Variables	Low load group	High load group	Statistical parameters	*P* value
Age [M (P25, P75), yr]	66 (57, 73)	70 (63, 76)	-1.632	0.105
Gender (Male/Female)	51/43	28/22	0.040[a]	0.841
Fasting blood glucose [M (P25, P75), mmol/L]	5.42 (4.94, 6.18)	5.6 (5.01, 7.33)	-1.154	0.249
TG [M (P25, P75), mmol/L]	1.6 (1.23, 1.88)	1.55 (1.36, 1.86)	-0.520	0.603
TC (mean ± SD, mmol/L)	3.88 ± 0.9	3.69 ± 1.11	1.054[b]	0.295
HDL-C (mean ± SD, mmol/L)	1.63 ± 0.78	1.85 ± 1.07	-1.276[b]	0.206
LDL-C (mean ± SD, mmol/L)	2.25 ± 0.66	2.11 ± 0.8	1.168[b]	0.245
HbA1c [M (P25, P75), %]	8.20 (7.12, 9.66)	8.99 (7.48, 9.90)	-1.452	0.147
Hcy [M (P25, P75) umol/L]	10.6 (8.33, 13.57)	11 (9.17, 13.93)	-0.913	0.361
CRP [M (P25, P75) mg/L]	2.35 (0.8, 4.3)	2.98 (1.1, 5.9)	-1.408	0.159
History of hypertension (*n*, %)	30 (31.9%)	24 (48%)	3.603[a]	0.058
History of coronary heart disease (*n*, %)	20 (21.3%)	14 (28%)	0.818[a]	0.366
Smoking history (*n*, %)	16 (17%)	11 (22%)	0.531[a]	0.466
Drinking history (*n*, %)	17 (18.1%)	12 (24%)	0.710[a]	0.399
BMI (mean ± SD, mmol/L)	24.78 ± 2.82	25.27 ± 2.29	-1.065[b]	0.289
SD (mean ± SD, mmol/L)	2.79 ± 0.37	3.15 ± 0.57	-3.949[b]	< 0.001
%CV (mean ± SD, %)	25.74 ± 4.1	31.02 ± 5.94	-5.615[b]	< 0.001
LAGE [M (P25, P75), mmol/L)]	9.94 (6.16, 12.27)	10.38 (6.79, 13.33)	-0.89	0.373
TIR [M (P25, P75), %)]	59.95 (49.18, 72.64)	43.2 (35.3, 51.24)	6.682	< 0.001

[a]Represents the χ^2 value.
[b]Represents the *t* value, and the remaining test statistic values are the Z value. TC: Total cholesterol; TG: Triglyceride; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; HbA1c: Glycosylated hemoglobin; Hcy: Homocysteine; CRP: C-reactive protein; BMI: Body Mass Index; SD: Standard deviation; %CV: Percentage coefficient of variation; LAGE: The largest amplitude of glucose; TIR: Time in range.

Table 2 Comparison of blood glucose variability indicators in different cognitive function groups

Group	Number	SD	%CV	LAGE	TIR
Cognitive dysfunction	37	3.15 ± 0.53	31.28 ± 5.38	10.35 (6.51, 13.49)	47.04 (37.61, 53.52)
Normal cognitive function	107	2.84 ± 0.44	26.29 ± 4.83	10.01 (6.34, 12.27)	56.02 (45.78, 69.46)
Statistical parameters		-3.513	-5.254	-0.738	3.825
P value		< 0.001	< 0.001	0.461	< 0.001

SD: Standard deviation; %CV: Percentage coefficient of variation; LAGE: The largest amplitude of glucose; TIR: Time in range.

glucose TIR was a protective factor for high lacune burden and cognitive impairment in lacune patients complicated with T2DM ($P < 0.05$; Table 3 and 4).

Predictive value of GV indicators for cognitive impairment in patients with lacunes complicated with T2DM

The ROC curve of cognitive impairment was drawn based on SD, %CV, and TIR (Figure 2), The area under the curve (AUC) of SD to predict cognitive impairment in patients with lacunes complicated with T2DM was 0.673 (95% confidence interval (CI): 0.565-0.781, $P < 0.01$). The optimal cut-off value was 3.018, the sensitivity was 64.9%, and the specificity was 68.2%. The AUC of %CV for predicting cognitive impairment was 0.757 (95%CI: 0.669-0.845, $P < 0.01$). The optimal cutoff value was 29.485%, the sensitivity was 67.6%, and the specificity was 74.8%. The AUC of TIR was 0.711 (95%CI: 0.623-0.799,

Table 3 Multivariate logistic regression analysis of the influencing factors on infarct burden in patients with lacunes complicated with type 2 diabetes mellitus

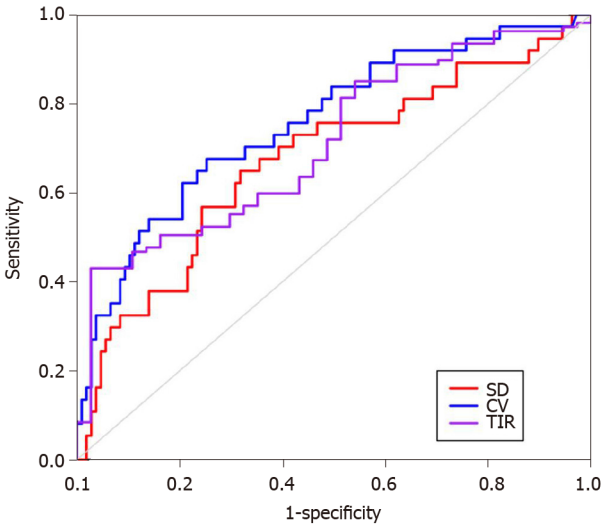
	β	SD	Wald	*P* value	OR	95%CI
SD	1.269	0.526	2.412	0.016	3.558	[1.268, 9.978]
%CV	0.176	0.05	3.527	< 0.001	1.192	[1.081, 1.315]
TIR	-0.129	0.028	-4.648	< 0.001	0.874	[0.833, 0.928]

SD: Standard deviation; %CV: Percentage coefficient of variation; TIR: Time in range.

Table 4 Multivariate logistic regression analysis of the influencing factors on cognitive impairment in patients with lacunes complicated with type 2 diabetes mellitus

	β	SD	Wald	*P* value	OR	95%CI
SD	0.919	0.465	1.976	0.048	2.506	[1.008, 6.230]
%CV	0.151	0.045	3.365	0.001	1.163	[1.065, 1.270]
TIR	-0.044	0.019	-2.253	0.024	0.957	[0.922, 0.994]

SD: Standard deviation; %CV: Percentage coefficient of variation; TIR: Time in range.



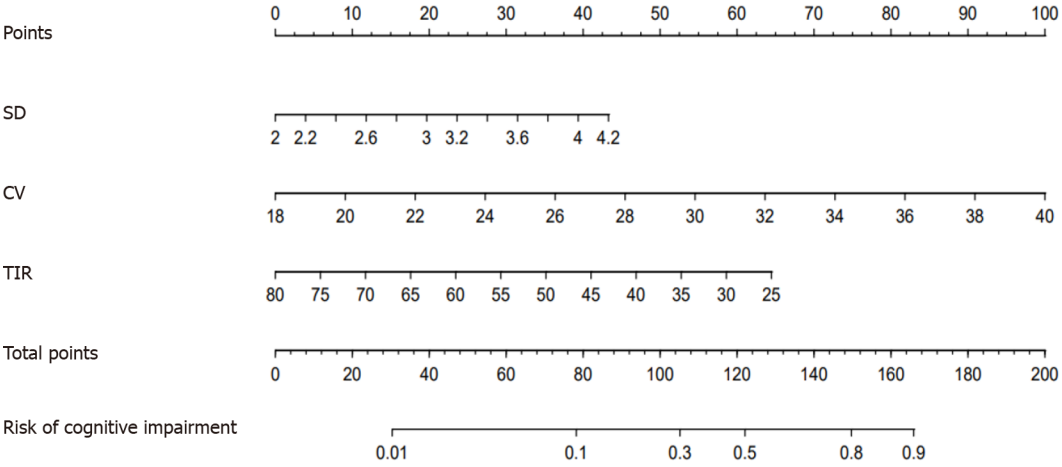
DOI: 10.12998/wjcc.v11.i5.1019

Figure 2 Receiver operating characteristic curve for glycemic variability in predicting cognitive impairment in patients with lacunes complicated with type 2 diabetes. SD: Standard deviation; %CV: Percentage coefficient of variation; TIR: Time in range.

P < 0.01). The optimal cut-off value was 60.5, the sensitivity was 97.3%, and the specificity was 43.0%. %CV and TIR had good clinical predictive value.

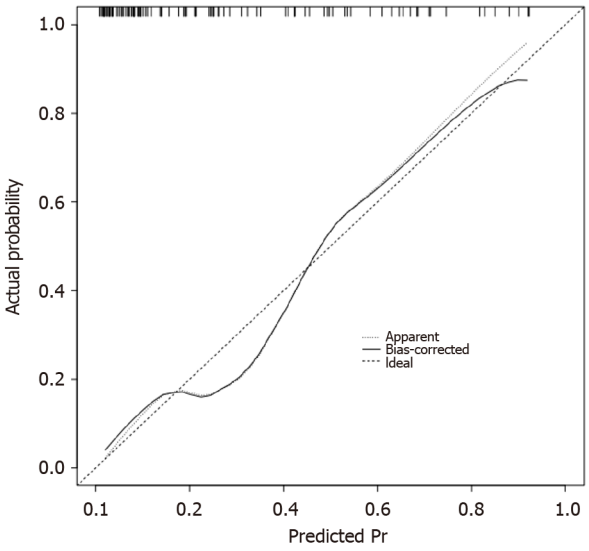
Establishment of a nomogram prediction model and the clinical benefit of testing for cognitive impairment in patients with lacunes complicated with T2DM

Based on SD, %CV, and TIR, a nomogram prediction model for cognitive impairment in patients with lacunes complicated with T2DM was established (Figure 3). The internal calibration analysis indicated how far the actual result is offset from the ideal result. An internal calibration analysis for this model showed that the actual result curve was similar to the corrected result curve and the ideal result curve, indicating that the actual prediction result of the model was similar to the ideal prediction result (Figure 4). The DCA for verification of the clinical benefit was performed and it could evaluate the clinical benefit and clinical predictive value of the model. The DCA of the model showed that the nomogram model curve was located on the upper right side of the two solid lines (the 'none' line and the 'all' line), indicating that the model had a greater clinical benefit and better clinical predictive value,



DOI: 10.12998/wjcc.v11.i5.1019

Figure 3 Nomogram model for predicting the risk of cognitive impairment in patients with lacunes complicated with type 2 diabetes. SD: Standard deviation; %CV: Percentage coefficient of variation; TIR: Time in range.



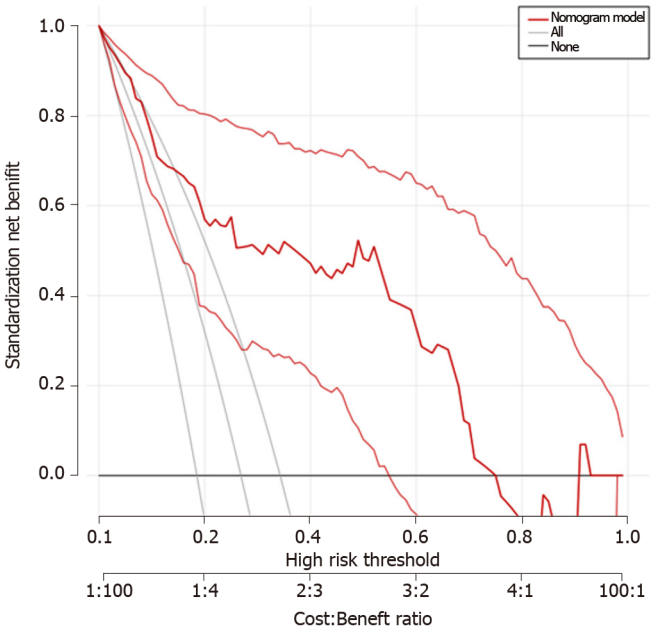
DOI: 10.12998/wjcc.v11.i5.1019

Figure 4 Internal calibration of the risk prediction model for cognitive impairment in patients with lacunes complicated with type 2 diabetes.

(Figure 5).

DISCUSSION

According to previous studies, the severity of lacunes is related to various factors, although the specific mechanisms remain unclear. It has been suggested that the main pathogenesis of lacunes is endothelial disorder and disruption of blood brain barrier (BBB)[2]; endothelial disorder is indicated to be the most important mechanism for lacunes[13]. The endothelium can regulate the tension of blood vessels, adjust fiber-dissolution or aggregation, participate in inflammatory responses, and participate in vascular wall formation[14]. Dysfunction of the endothelium reflects a shift towards promoting vasoconstriction, coagulation, inflammation, and increasing vessel thickness[15]. This can result in structural and functional damage to the endothelium, allowing the vessel walls to become leaky and inflamed. The autoregulatory function of the vessel wall is thereby impaired, preventing the vessel from dilating and reducing perfusion[16]. The normal vessel wall structure is gradually replaced by connective tissue, and the vessel wall thickens, resulting in lumen stenosis, thrombosis, and vascular occlusion[15,17]. GV is defined as variations in the blood glucose levels in a day or on different days, but the time remains the same. It contains elevated daily blood glucose levels, episodes of hyperglycemia, and hypoglycemia



DOI: 10.12998/wjcc.v11.i5.1019

Figure 5 Internal validation of the decision curve analysis of the nomogram prediction model for the risk of cognitive impairment in patients with lacunes complicated with type 2 diabetes.

[18]. TIR is a new convenient, intuitive, and easy to measure and understand indicator, that has been shown to predict the risk of long-term complications in diabetes. Diabetic complications can be caused by hyperglycemia, abnormal blood sugar levels, and fluctuations in blood sugar levels[19,20]. GV is closely related to arterial stiffness[9]. Furthermore, a cohort study in Taiwan, China, showed that GV had a positive correlation with ischemic stroke risk[21]. Japanese researchers reported that, especially in the postprandial state, excessive glucose fluctuations were positively associated with diabetic retinopathy and atherosclerosis[22]. These studies all suggest that changes in blood glucose fluctuation may affect the pathological progression of in lacune patients. T2DM is related to an increased risk of cognitive impairment. T2DM patients with high blood GV had increased cognitive decline[8]. According to this study, GV was an influencing factor for increased infarct burden in lacune patients combined with T2DM, and increased GV increased the risk of cognitive impairment in lacune patients complicated with T2DM. This suggests that the GV level of lacune patients with T2DM on admission should be detected to determine whether it will increase the burden of lacunes, increase the risk of cognitive impairment, and whether early clinical identification can be performed. Early treatment could prevent the occurrence and development of lacunes, and reduce the severity of lacunes, to improve prognosis and achieve glucose homeostasis in individuals with T2DM by regulating blood glucose fluctuations to reduce overall complications.

The influence of GV in the pathogenesis of infarct burden in lacune patients complicated with T2DM is not well understood. According to the previous research, blood GV has a significant impact on the progression and development of arterial endothelial disorder and atherosclerosis. Both hyperglycemia and hypoglycemia can damage brain structures. First, hyperglycemia can lead to changes in cerebral hemodynamics. One study found that the cerebral blood flow of hyperglycemic rats decreased by 37% compared with normal rats[23]. Second, vasodilation is mainly mediated by endothelial-derived nitric oxide, synthesized from endothelial nitric oxide synthase, the expression of which decreases in hyperglycemic environments[24]. Hyperglycemia can also increase reactive oxygen species (ROS) through a protease C mediated pathway increasing NADPH, resulting in neuronal deaths[25]. Furthermore, hyperglycemia is related to increased nuclear factor κB, which is found to stimulate inflammatory cell function, the production of inflammatory cytokines and endothelial damage, ultimately leading to increased damage and infarct area[26]. Hypoglycemia is also a factor that can aggravate cerebral ischemia. Severe hypoglycemia and mild hypoglycemia independently increased total mortality in patients with ischemic stroke[27]. Under hypoglycemic conditions (hunger-induced or insulin-induced), Ischemic brain cells showed increased energy metabolism and increased oxidative stress exposure[28]. Hyperglycemia and hypoglycemia worsen brain damage; however, importantly, when present with more dynamic glycemic control index, such as GV, it can be used to predict the lacune burden in lacune patients with T2DM more accurately and become an appropriate therapeutic target. The effect of GV on the burden of lacunes may be due to oxidative stress caused by elevated GV, triggering a surge of superoxide, leading to atherosclerosis[29]. Secondly, the increase of GV can lead to the enhanced adsorption of inflammatory factors and macrophages to vascular endothelial cells,

aggravating endothelial dysfunction[30]. Prolonged exposure to glucose instability can promote the ROS, aggravate oxidative stress and damage cellular DNA[31]. Finally, people with higher GV also have other dangerous elements such as hypertension and insulin resistance. The existence of these combined risk factors increases the risk of cerebrovascular events. The mechanism of GV affecting cognitive function may be that the above pathological changes result in damage to brain cells areas of cognitive function such as cerebellum, hippocampus, and frontal cerebral lobe. Furthermore the increase in blood GV leads to the damage of the BBB[32,33],and the increased production of ROS induces mitochondrial dysfunction, impaired oxidative stress, increased release of pro-inflammatory factors, and apoptosis[34, 35], these pathological changes lead to vascular injury in the central system of nerve[36]. Lacunes due to GV disrupts the network connections in the basal ganglia and dorsolateral prefrontal cortex. The lesions cleaved the fiber connections between several subcortical regions and the frontal cortex, prefrontal cortex and cingulate gyrus, which in turn inhibits functions related to cognition in the frontal cortex [37]. The destruction of cerebral vascular structure causes cerebral vascular autoregulation dysfunction, and can lead to the occurrence of amyloid angiopathy, which continuously reduces the cognitive function of patients, resulting in cognitive dysfunction[38]. In addition, increasing evidence has shown that the cerebellum is related to cognitive function, the prefrontal and the cerebellum cortex have extensive connections, and the cell damage of these connection could explain the cognitive decline in patients with cerebellar ischemia[8].

SD, %CV, LAGE, and TIR were used in this study describe the degree of GV more comprehensively and effectively in patients. Statistical analysis confirmed the close relationship between GV, lacunes burden and cognitive function in lacune patients with T2DM. In addition, a nomogram prediction model of GV index and lacunes complicated with T2DM patients with cognitive impairment was established, which could concisely and intuitively reflect the relationship between the risk of cognitive impairment in lacune patients complicated with T2DM and various risk factors.

However, this study has certain limitations. First, the calculation of indicators mainly relied on a single blood test after admission; therefore, the relative accuracy may be slightly lower, and there may be systematic errors, resulting in biased results. Second, the predictive model was only validated with internal data and lacks external validation. Finally, this study is a regression, single-center study, which may have selection bias.

CONCLUSION

In conclusion, there is a close relationship between GV and lacune burden in lacune patients with T2DM. Cognitive impairment in lacune patients complicated with T2DM is closely related to GV. In clinical practice, early assessment of GV indicators in patients with lacunes complicated with T2DM can increase early recognition of the severity and prognosis of lacunes, and improve TIR, which may be the key to preventing the occurrence and development of lacunes. By observing changes in the %CV, TIR and other indicators, they may aid in predicting the occurrence and development of cognitive disorder in patients. By strengthening the management of risk factors, we could significantly slow down the development of lacunes or reduce their severity and improve the prognosis.

ARTICLE HIGHLIGHTS

Research background

Lacunes and glucose variability (GV) are gaining growing attention.

Research motivation

The association between GV, the severity of lacunes and the cognitive impairment in lacune patients with type 2 diabetes mellitus (T2DM) is still unknown.

Research objectives

To explore the correlation between GV, lacune burden and cognitive function in patients with lacunes complicated with T2DM.

Research methods

Seventy-two h continuous blood glucose monitoring was performed. The Montreal cognitive assessment was used to assess cognitive function. The burden of lacunes was evaluated using magnetic resonance imaging findings. Multifactorial logistic regression analysis was used to study the affecting the lacune load and cognitive impairment in patients. To predict the value of patients' cognitive impairment with lacunes complicated with T2DM, a receiver operating characteristic curve and a nomogram prediction model were constructed.

Research results

Standard deviation and percentage coefficient of variation (%CV) were the risk factors for an increased infarct burden in lacune patients complicated with T2DM. Time of range (TIR) is a protective factor. In addition, an increased SD, %CV were the risk factors for cognitive impairment in patients with lacunes complicated with T2DM. TIR is a protective factor.

Research conclusions

Blood glucose variability is closely associated with the level of lacune burden and cognitive dysfunction in lacune patients combined with T2DM. %CV, TIR have a certain predictive effect in cognitive impairment in lacune patients.

Research perspectives

Prospective studies are further needed to verify the results of this paper.

FOOTNOTES

Author contributions: Meng QZ proposed the overall research goal and designed the research plan and model design; Yang XP conducted feasibility analysis, review and supervision of the experiment; Wang M, Li B, and Xiu JQ collected clinical data; Meng QZ and Wang Y conducted statistical processing and analysis of the data; Meng QZ and Xi Z are responsible for writing the first draft of the paper; Yang XP is responsible for the review, revision and quality control of the paper; all authors determined the final draft of the paper.

Supported by the Medical Technology and Science Research Project in Henan Province, China, No. SBGJ202102177.

Institutional review board statement: This study was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Zhengzhou University (2022031).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: We declare that we have no conflict of interest.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

ORCID number: Qi-Zhe Meng 0000-0003-0638-3754; Xiao-Peng Yang 0000-0002-2924-8785.

S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

REFERENCES

1 **Regenhardt RW**, Das AS, Stapleton CJ, Chandra RV, Rabinov JD, Patel AB, Hirsch JA, Leslie-Mazwi TM. Blood Pressure and Penumbral Sustenance in Stroke from Large Vessel Occlusion. *Front Neurol* 2017; **8**: 317 [PMID: 28717354 DOI: 10.3389/fneur.2017.00317]

2 **Caplan LR**. Lacunar infarction and small vessel disease: pathology and pathophysiology. *J Stroke* 2015; **17**: 2-6 [PMID: 25692102 DOI: 10.5853/jos.2015.17.1.2]

3 **Regenhardt RW**, Das AS, Lo EH, Caplan LR. Advances in Understanding the Pathophysiology of Lacunar Stroke: A Review. *JAMA Neurol* 2018; **75**: 1273-1281 [PMID: 30167649 DOI: 10.1001/jamaneurol.2018.1073]

4 **Wardlaw JM**, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, Lindley RI, O'Brien JT, Barkhof F, Benavente OR, Black SE, Brayne C, Breteler M, Chabriat H, Decarli C, de Leeuw FE, Doubal F, Duering M, Fox NC, Greenberg S, Hachinski V, Kilimann I, Mok V, Oostenbrugge Rv, Pantoni L, Speck O, Stephan BC, Teipel S, Viswanathan A, Werring D, Chen C, Smith C, van Buchem M, Norrving B, Gorelick PB, Dichgans M; STandards for ReportIng Vascular changes on nEuroimaging (STRIVE v1). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol* 2013; **12**: 822-838 [PMID: 23867200 DOI: 10.1016/S1474-4422(13)70124-8]

5 **Norrving B**. Long-term prognosis after lacunar infarction. *Lancet Neurol* 2003; **2**: 238-245 [PMID: 12849212 DOI: 10.1016/s1474-4422(03)00352-1]

6 **Umpierrez GE**, P Kovatchev B. Glycemic Variability: How to Measure and Its Clinical Implication for Type 2 Diabetes. *Am J Med Sci* 2018; **356**: 518-527 [PMID: 30447705 DOI: 10.1016/j.amjms.2018.09.010]

7 **Sparks JR**, Kishman EE, Sarzynski MA, Davis JM, Grandjean PW, Durstine JL, Wang X. Glycemic variability: Importance, relationship with physical activity, and the influence of exercise. *Sports Med Health Sci* 2021; **3**: 183-193 [PMID: 35783368 DOI: 10.1016/j.smhs.2021.09.004]

8 **Tang X**, Xiao X, Yin J, Yang T, Zeng B. An Assessment of the Relationship between Structural and Functional Imaging of Cerebrovascular Disease and Cognition-Related Fibers. *Comput Math Methods Med* 2020; **2020**: 4347676 [PMID: 32411283 DOI: 10.1155/2020/4347676]

9 **Zhang Y**, Wu S, Li M, Wang T, Xu M, Lu J, Wang S, Zhang J, Bi Y, Wang W, Ning G, Xu Y, Chen Y. Long-Term Glycemic Variability Is Associated With Arterial Stiffness in Chinese Adults. *Front Endocrinol (Lausanne)* 2021; **12**: 711540 [PMID: 34603201 DOI: 10.3389/fendo.2021.711540]

10 **Che YW**, Miao YW, Jiang YH, Chang PP, Song QW. A preliminary study of MRI of cerebral small vessel lesions in patients with systemic lupus erythematosus. [DOI: 10.1177/0961203308094361]

11 **Chinese Diabetes Society**. Guidelines for the prevention and control of type 2 diabetes in China (2017 edition). *Zhonghua Shiyongbingxue Zazhi* 2018; **38**: 292-344 [DOI: 10.1002/dmrr.3581]

12 **Hu WL**, Yang L, Li XT, Huang YH. Expert consensus on diagnosis and treatment of cerebral small vessel disease in China 2021. [DOI: 10.1002/brb3.2187/v2/decision1]

13 **Wardlaw JM**, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. *Lancet Neurol* 2013; **12**: 483-497 [PMID: 23602162 DOI: 10.1016/S1474-4422(13)70060-7]

14 **Wardlaw JM**, Doubal FN, Valdes-Hernandez M, Wang X, Chappell FM, Shuler K, Armitage PA, Carpenter TC, Dennis MS. Blood-brain barrier permeability and long-term clinical and imaging outcomes in cerebral small vessel disease. *Stroke* 2013; **44**: 525-527 [PMID: 23233386 DOI: 10.1161/STROKEAHA.112.669994]

15 **Poggesi A**, Pasi M, Pescini F, Pantoni L, Inzitari D. Circulating biologic markers of endothelial dysfunction in cerebral small vessel disease: A review. *J Cereb Blood Flow Metab* 2016; **36**: 72-94 [PMID: 26058695 DOI: 10.1038/jcbfm.2015.116]

16 **Giwa MO**, Williams J, Elderfield K, Jiwa NS, Bridges LR, Kalaria RN, Markus HS, Esiri MM, Hainsworth AH. Neuropathologic evidence of endothelial changes in cerebral small vessel disease. *Neurology* 2012; **78**: 167-174 [PMID: 22170884 DOI: 10.1212/WNL.0b013e3182407968]

17 **Bagi Z**, Brandner DD, Le P, McNeal DW, Gong X, Dou H, Fulton DJ, Beller A, Ngyuen T, Larson EB, Montine TJ, Keene CD, Back SA. Vasodilator dysfunction and oligodendrocyte dysmaturation in aging white matter. *Ann Neurol* 2018; **83**: 142-152 [PMID: 29283444 DOI: 10.1002/ana.25129]

18 **Gorst C**, Kwok CS, Aslam S, Buchan I, Kontopantelis E, Myint PK, Heatlie G, Loke Y, Rutter MK, Mamas MA. Long-term Glycemic Variability and Risk of Adverse Outcomes: A Systematic Review and Meta-analysis. *Diabetes Care* 2015; **38**: 2354-2369 [PMID: 26604281 DOI: 10.2337/dc15-1188]

19 **Beck RW**, Bergenstal RM, Riddlesworth TD, Kollman C, Li Z, Brown AS, Close KL. Validation of Time in Range as an Outcome Measure for Diabetes Clinical Trials. *Diabetes Care* 2019; **42**: 400-405 [PMID: 30352896 DOI: 10.2337/dc18-1444]

20 **Agiostratidou G**, Anhalt H, Ball D, Blonde L, Gourgari E, Harriman KN, Kowalski AJ, Madden P, McAuliffe-Fogarty AH, McElwee-Malloy M, Peters A, Raman S, Reifschneider K, Rubin K, Weinzimer SA. Standardizing Clinically Meaningful Outcome Measures Beyond HbA(1c) for Type 1 Diabetes: A Consensus Report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. *Diabetes Care* 2017; **40**: 1622-1630 [PMID: 29162582 DOI: 10.2337/dc17-1624]

21 **Lin CC**, Yang CP, Li CI, Liu CS, Chen CC, Lin WY, Hwang KL, Yang SY, Li TC. Visit-to-visit variability of fasting plasma glucose as predictor of ischemic stroke: competing risk analysis in a national cohort of Taiwan Diabetes Study. *BMC Med* 2014; **12**: 165 [PMID: 25255837 DOI: 10.1186/s12916-014-0165-7]

22 **Shichiri M**, Kishikawa H, Ohkubo Y, Wake N. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. *Diabetes Care* 2000; **23** Suppl 2: B21-B29 [PMID: 10860187]

23 **Quast MJ**, Wei J, Huang NC, Brunder DG, Sell SL, Gonzalez JM, Hillman GR, Kent TA. Perfusion deficit parallels exacerbation of cerebral ischemia/reperfusion injury in hyperglycemic rats. *J Cereb Blood Flow Metab* 1997; **17**: 553-559 [PMID: 9183293 DOI: 10.1097/00004647-199705000-00009]

24 **Ding Y**, Vaziri ND, Coulson R, Kamanna VS, Roh DD. Effects of simulated hyperglycemia, insulin, and glucagon on endothelial nitric oxide synthase expression. *Am J Physiol Endocrinol Metab* 2000; **279**: E11-E17 [PMID: 10893317 DOI: 10.1152/ajpendo.2000.279.1.E11]

25 **Suh SW**, Shin BS, Ma H, Van Hoecke M, Brennan AM, Yenari MA, Swanson RA. Glucose and NADPH oxidase drive neuronal superoxide formation in stroke. *Ann Neurol* 2008; **64**: 654-663 [PMID: 19107988 DOI: 10.1002/ana.21511]

26 **Bémeur C**, Ste-Marie L, Desjardins P, Vachon L, Butterworth RF, Hazell AS, Montgomery J. Dehydroascorbic acid normalizes several markers of oxidative stress and inflammation in acute hyperglycemic focal cerebral ischemia in the rat. *Neurochem Int* 2005; **46**: 399-407 [PMID: 15737438 DOI: 10.1016/j.neuint.2004.11.007]

27 **Krinsley JS**, Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcomes. *Crit Care Med* 2007; **35**: 2262-2267 [PMID: 17717490 DOI: 10.1097/01.CCM.0000282073.98414.4B]

28 **Chang YS**, Park WS, Ko SY, Kang MJ, Han JM, Lee M, Choi J. Effects of fasting and insulin-induced hypoglycemia on brain cell membrane function and energy metabolism during hypoxia-ischemia in newborn piglets. *Brain Res* 1999; **844**: 135-142 [PMID: 10536269 DOI: 10.1016/s0006-8993(99)01940-x]

29 **Ceriello A**, Esposito K, Piconi L, Ihnat MA, Thorpe JE, Testa R, Boemi M, Giugliano D. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. *Diabetes* 2008; **57**: 1349-1354 [PMID: 18299315 DOI: 10.2337/db08-0063]

30 **Ceriello A**, Ihnat MA. 'Glycaemic variability': a new therapeutic challenge in diabetes and the critical care setting. *Diabet Med* 2010; **27**: 862-867 [PMID: 20653741 DOI: 10.1111/j.1464-5491.2010.02967.x]

31 **Schisano B**, Tripathi G, McGee K, McTernan PG, Ceriello A. Glucose oscillations, more than constant high glucose, induce p53 activation and a metabolic memory in human endothelial cells. *Diabetologia* 2011; **54**: 1219-1226 [PMID: 21287141 DOI: 10.1007/s00125-011-2049-0]

32 **Hawkins BT**, Lundeen TF, Norwood KM, Brooks HL, Egleton RD. Increased blood-brain barrier permeability and altered tight junctions in experimental diabetes in the rat: contribution of hyperglycaemia and matrix metalloproteinases. *Diabetologia* 2007; **50**: 202-211 [PMID: 17143608 DOI: 10.1007/s00125-006-0485-z]

33 **Carey CL**, Kramer JH, Josephson SA, Mungas D, Reed BR, Schuff N, Weiner MW, Chui HC. Subcortical lacunes are associated with executive dysfunction in cognitively normal elderly. *Stroke* 2008; **39**: 397-402 [PMID: 18096844 DOI: 10.1161/STROKEAHA.107.491795]

34 **Quincozes-Santos A**, Bobermin LD, de Assis AM, Gonçalves CA, Souza DO. Fluctuations in glucose levels induce glial toxicity with glutamatergic, oxidative and inflammatory implications. *Biochim Biophys Acta Mol Basis Dis* 2017; **1863**: 1-14 [PMID: 27663722 DOI: 10.1016/j.bbadis.2016.09.013]

35 **Xue B**, Wang L, Zhang Z, Wang R, Xia XX, Han PP, Cao LJ, Liu YH, Sun LQ. Puerarin may protect against Schwann cell damage induced by glucose fluctuation. *J Nat Med* 2017; **71**: 472-481 [PMID: 28181078 DOI: 10.1007/s11418-016-1067-0]

36 **Hsieh CF**, Liu CK, Lee CT, Yu LE, Wang JY. Acute glucose fluctuation impacts microglial activity, leading to inflammatory activation or self-degradation. *Sci Rep* 2019; **9**: 840 [PMID: 30696869 DOI: 10.1038/s41598-018-37215-0]

37 **Yoon CW**, Seo SW, Park JS, Kwak KC, Yoon U, Suh MK, Kim GH, Shin JS, Kim CH, Noh Y, Cho H, Kim MJ, Kim JH, Roh JH, Lee JM, Na DL. Cerebellar atrophy in patients with subcortical-type vascular cognitive impairment. *Cerebellum* 2013; **12**: 35-42 [PMID: 22538732 DOI: 10.1007/s12311-012-0388-0]

38 **Qi Q**, T Yi, Jia JP. P1-181: Amyloid beta oligomers involved in cognitive impairment by ngr-rhoa-rock pathway mediated inhibition of t-type calcium channels. *Alzheimer's & Dementia* 2019; **15**: 7S [DOI: 10.1016/j.jalz.2019.06.736]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com