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Effect of Blood Glucose Gap on Post-stroke Cognitive Impairment in Acute Ischemic Stroke Patients

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Abstract: *Objective*: To analyze the effect of the blood glucose gap on post-stroke cognitive impairment in acute ischemic stroke patients. *Methods*: 300 stroke patients admitted to the hospital between December 2021 and December 2022 were selected and divided into three groups according to the value of blood glucose gap: the group with no elevation of blood glucose gap (n = 124), the group with mild elevation of blood glucose gap (n = 97), and the group with elevated blood glucose gap (n = 79). The same treatment regimen was applied to these three groups and cognitive function was assessed using MMSE and MoCA at 3, 6, and 12 months after discharge. *Results*: The NIHSS and MoCA scores of the patients in the group with elevated blood glucose gap were significantly higher than those in the mildly elevated group and the non-elevated group at 3, 6, and 12 months after discharge, and the MMSE and MoCA scores of the patients in the group with mildly elevated blood glucose gap were significantly higher than those in the non-elevated group at 3, 6, and 12 months after discharge, and there were statistically significant differences between all the groups ($P < 0.05$). *Conclusion*: Patients with an elevated glycemic gap in acute ischemic stroke showed more pronounced cognitive impairment than those with no elevated glycemic deficit, and the severity of cognitive impairment increased with the degree of glycemic deficit.

Keywords: Glycemic gap; Acute ischemic stroke; Cognitive impairment

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1. Introduction

The significant impact of hyperglycemia on patient prognosis is widely recognized in a wide range of conditions, particularly in the prognostic assessment of conditions such as acute ischemic stroke, sepsis, and polytrauma, and its predictive value has been confirmed in several studies. However, the manifestation of this phenomenon in individuals does not necessarily correlate with a history of diabetes. It may arise from the occurrence of acute hyperglycemia in diabetic patients, or high baseline blood glucose due to acute physiological stress, or both of these factors may be present at the same time. This complexity adds to the difficulty of assessment to some extent. Recent studies have suggested that relying solely on hyperglycemia as a prognostic predictor may be subject to multiple biases, and have therefore introduced the concept of a "glycemic gap." The glycemic gap is defined as a significant increase in blood glucose levels during stress [1]. This concept provides a new perspective

to better understand and assess the impact of hyperglycemia on patient prognosis. ΔBG represents the difference between the blood glucose level on admission and the chronic blood glucose level (CBG), which is derived from the conversion of HbA1c. In the current diagnosis and prevention of post-stroke cognitive impairment (PSCI), biological indicators of Alzheimer's disease (AD), such as A-protein and tau protein, are usually introduced to support the diagnosis or prediction. However, the use of these indicators for accurate and early determination of PSCI is difficult and has low patient acceptance. Recent studies have found that the blood glucose gap can be applied by simply measuring glycated hemoglobin and blood glucose levels on admission and then deriving them by simple conversion, a method that is not only simple and convenient but also has obvious advantages in terms of wider application. However, literature is scarce on the use of the blood glucose gap in the analysis and prediction of PSCI, so this study aims to analyze and discuss this issue in depth.

2. General information and methods

2.1. General information

The target population of this study was 300 cases of acute ischemic stroke, 165 males and 135 females, who attended the hospital between December 2021 and December 2022. The age range of the patients was 41 to 70 years with a mean age of 52.34 ± 10.23 years. The time interval from onset to consultation ranged from 1 hour to 2 hours with a mean time of 1.45 ± 0.37 hours. All cases participating in the study met the diagnostic criteria listed in the Chinese Expert Consensus on Emergency Diagnosis and Treatment of Acute Ischemic Stroke in Chinese and Western Medicine.

2.2. Inclusion and exclusion criteria

Inclusion criteria: Patients with acute ischemic stroke within 7 days of onset were included according to the 2018 Chinese Acute Ischemic Stroke Diagnosis and Treatment Guidelines and etiologically typed according to TOAST typing.

Exclusion criteria: (1) those who were unwilling to attend; (2) those who had any mental abnormality, difficulty in verbal communication, and whose family members did not cooperate or were unable to follow up for other reasons; (3) those who were accompanied by tumors or severe liver or renal insufficiency; and (4) those who had acute infections.

2.3. Grouping method

At the time of admission, the relevant hematological indexes of acute ischemic stroke cases were collected and grouped based on the blood glucose gap. Among them, cases with a blood glucose gap of 0 were classified as the non-elevated group; cases with a blood glucose gap between 0 and 2.78 mmol/L were classified as the mildly elevated group; and cases with a blood glucose gap of more than 2.78 mmol/L were classified as the elevated group [2].

2.4. Observation indicators

After the same treatment, the discharge time and follow-up time are set according to the actual situation of the cases.

2.4.1. NIHSS assessment

A rating scale was used to assess the degree of neurological deficit in acute ischemic stroke. The scale consists of several items and is mainly used to assess various aspects of neurological function such as the patient's level

of consciousness, language, motor ability, sensation, visual field, and coordination. The NIHSS was assessed at admission, 3 months, 6 months, and 12 months after discharge to regularly evaluate the treatment effect and thus to grasp the recovery progress of the cases. The NIHSS scores ranged from 0 to 42, with higher scores indicating more severe neurological damage. The specific grading criteria are: "0–1" indicates normal or nearly normal; "1–4" indicates mild stroke; "5–15" indicates moderate stroke; a score of "15–20" indicates a moderately severe stroke state; a score of "21–42" indicates a severe stroke state.

2.4.2. MoCA assessment

The MoCA scale is a cognitive assessment tool specifically designed to screen for mild cognitive impairment, covering multiple dimensions such as calculation, language, orientation, memory, attention and concentration, and executive function, with a full score of 30. When the score reaches 26, it is considered normal. MoCA was assessed at admission, 3 months, 6 months, and 12 months after discharge for the three groups of cases. Determination of postoperative cognitive disability (POCD) was achieved by the Newman method. The steps of this method were to compare the preoperative and postoperative MoCA test results with the standard deviation of the preoperative MoCA cognitive function score as a control. By calculating the difference between the preoperative and postoperative scores, the condition of POCD was considered to be fulfilled when the difference in more than one dimension exceeded one standard deviation.

2.5. Statistical methods

SPSS 16.0 statistical software was used to complete the analysis of statistical results. Measurement data obeying normal distribution were described by mean ± SD, and independent samples *t*-test was used for comparison between groups; while skewed distribution measurement data were described by median (M) [Interval of Quartiles (IQR)], and Mann-Whitney *U*-test was used for comparison between groups. The counting data were expressed as percentages, and the x^2 test was used for comparison between groups. Comparisons between groups were made using the x^2 test; correlation analyses between the two groups were performed using Pearson or Spearman; and analyses were performed using dichotomous multifactorial and unordered multi-categorical multifactorial logistic regression.

3. Results

3.1. Comparison of general information of patients in three groups

In this study, patients were grouped according to different blood glucose gap values, of which 124 patients with normal ΔBG accounted for 41.33% of the total number; 97 patients with mildly elevated ΔBG accounted for 32.33% of the total number; and 79 patients with significantly elevated ΔBG accounted for 26.33% of the total number.

A comparison of the general data of the three groups showed that no significant differences were found in age, gender, and NIHSS score on admission ($P > 0.05$), except for a statistical difference in blood glucose gap values ($P < 0.05$). This indicates that the three groups of patients in this study were feasible and balanced in the later study. The specific data are shown in **Table 1**.

Table 1. Comparison of general data of the three groups of patients

Project/Groups	Group with non-elevated blood glucose gap (n = 124)	Group with mildly elevated blood glucose gap (n = 97)	Group with elevated blood glucose gap (n = 79)
Age (years)	52.16 ± 9.78	52.33 ± 9.89	52.43 ± 10.25
Sex (male, n %)	57 (34.55%)	53 (32.12%)	55 (33.33%)
Blood glucose gap (mmol/L)	-0.35 ± 0.09	2.45 ± 0.89	3.03 ± 1.12
NIHSS at admission (points)	26.9 ± 7.61	26.4 ± 8.01	26.7 ± 7.89
MoCA at admission (points)	28.37 ± 0.43	28.19 ± 0.36	28.32 ± 0.40
Time from onset to consultation (h)	1.40 ± 0.40	1.47 ± 0.42	1.43 ± 0.39

3.2. NIHSS assessment and comparison at admission, 3 months, 6 months, and 12 months after discharge

At the time of admission, there was no significant difference ($P > 0.05$) in the comparison of NIHSS assessment results among the three groups of patients, as shown in **Table 1**.

It was found that the NIHSS scores of patients in the group with elevated blood glucose gap were significantly higher than those in the mildly elevated and non-elevated groups at 3, 6, and 12 months after discharge. In addition, patients in the mildly elevated blood glucose gap group also had significantly higher NIHSS scores than those in the non-elevated group at 3, 6, and 12 months after discharge. There was a statistically significant difference between all groups ($P < 0.05$). The detailed data are shown in **Table 2**.

Table 2. Comparison of neurological function NIHSS scores before and after treatment in the three groups (points, mean ± SD)

Groups	On admission	After discharge		
		3 months after discharge	6 months after discharge	12 months after discharge
Group with non-elevated blood glucose gap (n = 124)	26.9 ± 7.61	14.2 ± 3.41	9.2 ± 3.23	6.2 ± 2.56
Group with mildly elevated blood glucose gap (n = 97)	26.4 ± 8.01	17.2 ± 4.10	11.2 ± 3.67	10.56 ± 3.76
Elevated blood glucose gap group (n = 79)	26.7 ± 7.89	25.4 ± 5.87	23.8 ± 4.89	22.4 ± 5.87
F/χ^2	0.321	3.511	4.245	5.232
P	0.786	0.043	0.039	0.033

3.3. Assessment and comparison of MoCA at admission, 3 months, 6 months, and 12 months post-discharge

At the time of admission, there was no significant difference ($P > 0.05$) in the comparison of MoCA assessment results among the three groups of patients, as shown in **Table 1**.

It was found that the MoCA scores of patients in the group with elevated blood glucose gap were significantly higher than those in the mildly elevated and non-elevated groups at 3, 6, and 12 months after discharge. Also, patients in the mildly elevated blood glucose gap group had significantly higher MoCA scores than the non-elevated group at 3, 6, and 12 months post-discharge. There was a statistically significant difference between all groups ($P < 0.05$). The detailed data are shown in **Table 3**.

Table 3. Comparison of neurological function MoCA scores before and after treatment in the three groups (points, mean ± SD)

Groups	On admission	After discharge		
		3 months after discharge	6 months after discharge	12 months after discharge
Group with non-elevated blood glucose gap (n = 124)	28.37 ± 0.43	16.46 ± 0.68	12.65 ± 0.57	8.46 ± 0.48
Group with mildly elevated blood glucose gap (n = 97)	28.19 ± 0.36	20.46 ± 0.73	16.23 ± 0.46	14.46 ± 0.48
Elevated blood glucose gap group (n = 79)	28.32 ± 0.40	26.46 ± 0.53	23.46 ± 0.40	20.46 ± 0.48
F/x^2	0.354	3.864	4.432	5.287
P	0.845	0.045	0.036	0.031

4. Conclusion

In recent years, the incidence and mortality rates of stroke have remained high in China and have attracted increasing attention because of its tendency to cause disability and recurrence [3–6]. Once a stroke occurs, the lives and health of patients will be seriously affected. Among the many complications of stroke, post-stroke cognitive impairment is particularly prominent and extremely harmful. Therefore, early prevention and timely diagnosis and treatment become key factors. For post-stroke cognitive impairment (PSCI), glycemic parameters such as hyperglycemia, glycemic variability, glycated hemoglobin, and glycemic kinetics are considered potential risk factors [7–9]. Studies have shown that hyperglycemia may impair cognitive function after stroke through several mechanisms. These mechanisms include increasing the production of reactive oxygen species, causing mitochondrial dysfunction, and triggering an inflammatory response, which ultimately leads to secondary neuronal damage, thus affecting the cognitive ability of patients. The studies of some scholars found that the indicator of mortality was significantly higher in the group with severely elevated blood glucose levels than in the group with mildly elevated levels and the normal group, and this difference was statistically significant [10–12]. After logistic regression analysis, a key conclusion can be drawn: the new indicator of the blood glucose gap can effectively reflect changes in response to stressful blood glucose. Meanwhile, the blood glucose gap has also been shown to predict the prognosis of limb function in post-stroke patients, but its relationship with post-stroke cognitive impairment (PSCI) still lacks clear research results [10]. Therefore, further exploration of the association between the blood glucose gap and PSCI will provide a richer basis for comprehensive management and treatment strategies for stroke patients.

The results of this study showed that patients in the mildly elevated glycemic gap group had significantly higher MMSE and MoCA scores than those in the non-elevated group at 3, 6, and 12 months after discharge, with statistically significant differences in all group comparisons ($P < 0.05$). These results suggest that an elevated blood glucose gap in acute ischemic stroke patients is significantly associated with increased cognitive impairment after stroke. There may be several reasons for this phenomenon: (1) Hyperglycemia and its variability may lead to increased inflammatory response, and this inflammation not only affects the microvascular function of the brain but may also lead to neuronal damage and death. (2) Elevated blood glucose gaps may be associated with oxidative stress, and the increase in reactive oxygen species may be toxic to cells, which in turn may affect the normal functioning of the nervous system. (3) Blood glucose fluctuations may affect the energy metabolism of the brain, resulting in nerve cells being unable to function properly with insufficient energy supply, thus exacerbating the manifestations of cognitive impairment. The occurrence of cognitive impairment worsened

as the degree of elevation of the blood glucose gap increased, suggesting that glycemic stability is critical to the cognitive health of stroke patients. Therefore, increased attention to glycemic management and effective measures to control glycemic fluctuations in the clinic can help improve the cognitive prognosis of patients and provide stronger support for stroke patients' recovery.

In summary, the blood glucose gap is defined as the difference between admission blood glucose and mean blood glucose, and as an emerging biomarker, it has important clinical significance in patients with acute ischemic stroke. Studies have shown that an elevated blood glucose gap is not only strongly associated with the incidence of post-stroke cognitive impairment, but may also be one of its predictors. A high blood glucose gap may reflect dramatic fluctuations in blood glucose levels, which can lead to intrinsic metabolic imbalance and oxidative stress in the body, further aggravating brain tissue damage and neuronal dysfunction. Therefore, by monitoring the blood glucose gap, clinicians can better assess the cognitive risk of patients and inform optimal post-stroke management.

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Disclosure statement

The authors declare no conflict of interest.

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