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Original Article

Fasting blood glucose levels affect hospitalization time and relapse and mortality rates of cerebral infarction patients

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Abstract: Objective: This study determined the relationship between fasting glucose levels of cerebral infarction patients and the hospitalization time and relapse and mortality rates. Methods: A retrospective study was conducted between February 1996 and December 2006 involving 974 inpatients with cerebral infarctions. Fasting blood glucose and lipid levels and blood pressure were measured the morning after hospitalization. The length of hospital stay, and data obtained from telephone follow-up interviews regarding relapse and complications were recorded. The data were analyzed using multiple linear regressions, logistic regression, the chi-square test, and the Kruskal-Wallis analysis of variance of ranks test. Results: Our data show that the duration of hospitalization and relapse and mortality rates of patients with cerebral infarctions correlate with the admission fasting blood glucose levels. Cerebral infarction patients with fasting blood glucose levels > 11.1 mmol/L and LDL levels > 3.5 mmol/L have higher mortality rates (50.00%). Patients with fasting blood glucose levels > 11.1 mmol/L combined with a diastolic pressure < 80 mmHg or > 100 mmHg also have high mortality rates (33.33% and 30.00%, respectively). Conclusions: Fasting glucose levels of inpatients with cerebral infarctions are closely related to the duration of hospitalization and relapse and mortality rates. Higher fasting blood glucose levels exacerbate damage to cerebral blood vessels caused by alterations in blood lipid levels and blood pressure. Therefore, blood glucose levels should be monitored during the early stage of cerebral infarction and intervention should be provided promptly to decrease the length of hospital stay and the risk of relapse and mortality.

Keywords: Cerebral infarction, blood glucose, relapse, mortality

Introduction

Cerebral infarctions are often associated with elevated blood glucose levels. Several recent studies have shown that hyperglycemia exacerbates brain damage in cerebral infarction patients, increases the mortality rate of inpatients, and affects the clinical prognosis [1-3]. To provide support for glucose-reducing interventions, we conducted a retrospective study of the clinical data from 974 patients with cerebral infarctions and determined the effects of fasting blood glucose and lipid levels and blood pressure on relapse and mortality rates in these patients.

Subjects and methods

Research subjects

We selected 974 cerebral infarction patients who were hospitalized in the Neurology Department of our hospital between February 1996 and December 2006. Computed tomography (CT) or magnetic resonance imaging (MRI) of the brain confirmed that all research subjects met the diagnostic standards for cerebral infarction made by the Chinese Cerebrovascular Disease Association. We chose patients with arterothrombtic cerebral infarctions and no limitations on the localization of the infarctions, concomitant symptoms, or complications. Within the subject group, there were 646 males and 328 females (age range, 31-98 years; average age, 67.0 ± 11.6 years).

Methods

Collection of clinical data: The onset of the disease, date of hospital admission, and duration of hospitalization were recorded and the blood pressure levels were determined for all patients. The morning after admission, we measured fasting blood glucose (using the glucose oxi-

Table 1. Relationship between fasting glucose levels and relapse, length of hospitalization, and mortality

Fasting glucose concentration (mmol/L)	Percentage (%)	Average hospitalization time (d)	Mortality (%)	Relapse (%)
≤ 5.5	548 (56.26)	21.15 ± 10.78	19 (3.47)	42 (7.66)
5.6-6.0	115 (11.81)	26.03 ± 11.15[a]	5 (4.35)[a]	17 (14.78)[a]
6.1-6.9	122 (12.53)	27.08 ± 10.93[b]	8 (6.56)[b]	35 (28.69)[b]
7.0-11.1	156 (16.02)	28.51 ± 10.40[c]	15 (9.64)[c]	57 (36.53)[c]
≥ 11.1	33 (3.39)	30.45 ± 12.84[d]	8 (24.24)[d]	13 (39.39)[d]

Compared to blood glucose ≤ 5.5 mmol/L, [a]$P < 0.05$; compared to blood glucose 5.6-6.0 mmol/L, [b]$P < 0.05$; compared to blood glucose 6.1-6.9 mmol/L, [c]$P < 0.05$; compared to blood glucose 7.0-11.1 mmol/L, [d]$P < 0.05$.

Table 2. Clinical data of diabetic and non-diabetic patients

General information	Diabetes group	Non-diabetes group
Percentage (%)	241 (24.74)	733 (75.26)
FPG (mmol/L)	7.90 ± 2.70*	5.38 ± 1.40
Average hospitalization time	25.17 ± 13.77	23.57 ± 10.51
Mortality (%)	13 (5.39)	42 (5.73)
Relapse (%)	68 (41.46)*	96 (13.10)

Compare the two groups, *$P < 0.001$.

Table 3. Clinical data of diabetic and non-diabetic hyperglycemia patients

General information	Diabetes group	Non-diabetes hyperglycemia group
Percentage (%)	241 (24.74)	222 (72.79)
Male (%)	139 (57.68)	144 (64.86)
Female (%)	102 (42.32)	78 (35.14)
Age (year)	68.40 ± 9.55	68.65 ± 11.92
SBP (mmHg)	148.68 ± 20.29	144.95 ± 20.92
DBP (mmHg)	85.05 ± 11.42	86.06 ± 12.54
FPG (mmol/L)	7.90 ± 2.70*	6.72 ± 1.75
TG (mmol/L)	1.84 ± 1.69	1.86 ± 1.51
TC (mmol/L)	4.98 ± 1.31	5.08 ± 1.27
LDL (mmol/L)	3.03 ± 0.91	3.05 ± 0.88
HDL (mmol/L)	1.05 ± 0.28	1.08 ± 0.27
Average hospitalization time	25.17 ± 13.77	29.05 ± 14.77**
Mortality (%)	13 (5.39)	16 (7.21)**
Relapse (%)	68 (41.46)	55 (24.77)*

Compare the two groups, *$P < 0.001$; **$P < 0.01$.

dase method), total cholesterol (TC), triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C) levels.

Telephone follow-up: All of the research subjects had one telephone follow-up call between December 2007 and April 2008 to ascertain the incidence of relapse and whether or not diabetes and/or hypertension had been diagnosed.

The characteristics of blood lipid profiles were categorized according to the following parameters: fasting blood glucose level (≤ 5.5, 5.6-6.0, 6.1-6.9, 7.0-11.1, and ≥ 11.1 mmol/L); TG, (< 1.0, 1.0-1.7, and ≥ 1.7 mmol/L); TC (< 4.5, 4.5-5.5, and ≥ 5.5 mmol/L); LDL-C (< 2.5, 2.5-3.5, and ≥ 3.5 mmol/L); HDL-C (≤ 1.04 mmol/L and > 1.04 mmol/L); systolic blood pressure (SBP; ≤ 130, 130-160, 160-180, and ≥ 180 mmHg [1 mmHg = 0.133 kPa]); and diastolic blood pressure (DBP; ≥ 100, 90-100, 80-90 and ≤ 80 mmHg).

Statistical analysis

Statistical analysis was performed using SAS 8.2 software. The relationships among all factors, the time to relapse, and the length of hospitalization were analyzed using multiple linear regression. The association with mortality rate was analyzed by logistic regression. A factor was considered a risk factor when the odds ratio (OR) was > 1. The chi-square test was used to compare the mortality rates after cross-classification of blood glucose and lipid levels and blood pressure, while the Kruskal-Wallis test was used for the time to relapse and the length of hospitalization. A $P < 0.05$ defined statistically significant differences.

Results

Basic clinical information

Among the 974 subjects, 241 (24.74%) were diagnosed with diabetes, 222 (22.79%) had abnormal fasting blood glucose levels (≥ 5.6 mmol/L), 632 (64.89%) had hypertension, 393 (40.35%) had TG ≥ 1.7 mmol/L, 384 (39.43%) had TC ≥ 5.2 mmol/L, 415 (42.61%) had LDL-C ≥ 3.12 mmol/L, and 474 (48.67%) had HDL-C ≤ 1.04 mmol/L. The average length of hospital stay was 24.0 ± 21.2 days, and the average fasting glucose level was 6.0 ± 2.1 mmol/L. One hundred sixty-four patients (16.84%) had relapses and 55 patients died (5.65%).

Relationship between fasting glucose levels and relapse, length of hospitalization, and mortality

Interestingly, in our subject group the fasting glucose levels were not associated with diabetes. Based on our data, the fasting blood glucose levels of cerebral infarction patients at the time of hospital admission were positively correlated with the number of relapses (R = 0.1238, t = 7.84, P < 0.01), length of hospitalization (R = 3.0693, t = 4.69, P < 0.01), and mortality (R = 0.6701, OR = 1.954, 95% CI: 1.522-2.510). The duration of hospitalization and relapse and mortality rates increased in patients with fasting glucose levels were elevated (**Table 1**). The rate of relapse in patients with diabetes was significantly higher than patients without diabetes (41.46% and 13.10%, respectively; P < 0.01; **Table 2**). Patients with abnormal fasting glucose levels (≥ 5.6 mmol/L) remained in the hospital longer on average than patients with diabetes (29 ± 15 and 25 ± 14 days, respectively; P < 0.01). Patients with abnormal fasting glucose levels also had a higher mortality rate than patients with diabetes (7.21% and 5.39%, respectively; P < 0.01; **Table 3**). Therefore, whether or not patients with diabetes had increased fasting blood glucose levels at the time of hospital admission is a predictive factor for relapse of cerebral infarction.

Relationship between blood lipid levels and relapse, length of hospitalization, and mortality

The blood lipid levels of cerebral infarction patients at the time of hospital admission did not correlate with the number of relapses (TG: R = -0.0169, t = -1.01, P > 0.05; TC: R = 0.0285, t = 0.91, P > 0.05; LDL-C: R = -0.0310, t = -0.84, P > 0.05; HDL-C: R = -0.0252, t = -0.39, P > 0.05). Thus, hyperlipidemia cannot be considered a predictive factor for relapse of cerebral infarction. There was no significant correlation between blood lipid levels and the duration of hospitalization (TG: R = -0.9323, t = -1.34, P > 0.05; TC: R = 1.2371, t = 0.95, P > 0.05; LDL-C: R = -1.5193, t = -1.00, P > 0.05; HDL-C: R = -0.9099, t = -0.34, P > 0.05). The mortality rate positively correlated with the levels of LDL-C (R = 1.0754, OR = 1.341, 95% CI: 1.154-1.754) and TG (R = 0.5487, OR = 1.578, 95% CI: 1.350-1.952), but did not correlate with the levels of TC (R = 0.6254, OR = 1.968, 95% CI: 0.942-3.707) and HDL-C (R = 0.3609, OR = 1.435, 95% CI: 0.460-4.472).

Relationship between blood pressure level and relapse, length of hospitalization, and mortality

The SBP and DBP of the cerebral infarction patients at the time of hospital admission were not significantly associated with relapse (SBP: R = -0.0003, t = -0.30, P > 0.05; DBP: R = 0.0033, t = 1.75, P > 0.05), duration of hospital stay (SBP: R = -0.0079, t = -0.17, P > 0.05; DBP: R = 0.0422, t = 0.54, P > 0.05), or mortality (SBP: R = 0.0018, OR = 1.002, 95% CI: 0.982-1.022; DBP: R = 0.0111, OR = 1.011, 95% CI: 0.979-1.045).

Combined effects of fasting blood glucose and blood lipid levels on cerebral infarction

After cross-classification based on fasting glucose and blood lipid levels, we showed that the duration of hospitalization and mortality rate of the patients tended to increase when the fasting blood glucose and TC levels were elevated. Patients with fasting glucose levels > 11.1 mmol/L and TC levels > 5.5 mmol/L had the longest hospital stays (38 ± 24 d; P < 0.01) and highest mortality rate (33.33%; P < 0.01). Patients with fasting blood glucose levels > 11.1 mmol/L and LDL-C levels > 3.5 mmol/L had a significantly higher mortality rate (50.00%, P < 0.01). In conclusion, increased fasting glucose levels combined with elevated TC and LDL-C levels may be an important risk factor for cerebral infarction.

Combined effects of a fasting blood glucose level and blood pressure on cerebral infarction

Cross-classification based on a fasting glucose level and blood pressure showed that patients with a fasting blood glucose level > 11.1 mmol/L combined with a DBP that was either < 80 mmHg or > 100 mmHg had an increased mortality rate (33.33% and 30.00%, respectively, $P < 0.01$). The duration of hospitalization and the number of relapses, however, were not significantly related to the combined effects of the two factors.

Discussion

Diabetes is a major risk factor for cerebral infarction. Studies have shown that diabetes and elevated fasting blood glucose levels are closely associated with ischemic stroke and other macrovascular events [4, 5]. Diabetes patients have a higher occurrence of cerebral infarction, exhibit more severe infarction phenotypes, and have a worse prognosis than non-diabetic patients. A long period of hyperglycemia in diabetes patients can accelerate the progression of atherosclerosis and cause multiple complications, and also exacerbate the damage done to the nervous system during a cerebral infarction. Among the 974 patients in this study, approximately one-fourth had type 2 diabetes and nearly one-half had abnormal fasting blood glucose levels.

Cerebral infarction patients often have hyperglycemia [6]. It has been shown that fasting blood glucose levels are linearly correlated with the risk for ischemic stroke and myocardial infarction [7]. The risk for ischemic stroke increases significantly when blood glucose levels are > 5.6 mmol/L, while the risk for myocardial infarction and hemorrhagic stroke increases when blood glucose levels are > 7.5 mmol/L. We found that patients with abnormal fasting blood glucose levels (≥ 5.6 mmol/L) stay longer in the hospital and have increased rates of relapse and mortality. A plausible explanation for these findings could be that hyperglycemia decreases regional cerebral blood flow, increases the infarct area, and accelerates the accumulation of lactic acid in ischemic cerebral tissues. The damage of the brain may be caused by multiple mechanisms, as follows: acidosis and disrupted balance of calcium levels; mitochondria damage; disrupted balance of coagulation and the fibrinolysis system; damage of regional microcirculation; induce oxidative stress and inflammation responses; disrupted integrity of the blood-brain barrier that leads to increased permeability; and local brain tissue edema [8-10].

Based on our findings, fasting blood glucose levels obtained during the early stage of the disease can be used for estimating the affected area and the prognosis, and control of blood glucose levels may be essential to minimize brain damage. In summary, this study showed that fasting blood glucose levels can be used as an important predictive factor for relapse and mortality during hospitalization in cerebral infarction patients.

An interesting finding of this study was that diabetes is not significantly related to the length of hospitalization or mortality, which may be due to the following reasons: (1) Diabetic patients may already have undergone routine glucose-reducing treatments, such as lifestyle interventions, oral medications, and insulin, that control blood glucose levels. (2) Diabetic patients received glucose-reducing treatments during hospitalization due to the disease history. (3) Diabetes is often associated with hyperlipidemia, hypertension, and macrovascular diseases, such as coronary heart disease. Patients may have been taking lipid-reducing, anti-hypertensive, or anti-platelet treatments before cerebral infarction, thus making the fasting blood glucose levels upon hospitalization artificially low. (4) Patients may have had undiagnosed diabetes, and therefore were not treated promptly. In this study, some “non-diabetic” patients may have developed diabetes too recently to be diagnosed before the cerebral infarction event. Such patients have hyperglycemia, severe infarction phenotypes, and a poor prognosis. Therefore, special attention should be paid to non-diabetic patients with hyperglycemia. A previous study showed that at a plasma glucose threshold level of 11.7 mmol/L, the diagnosis of diabetes had a specificity of 90.0% and a positive rate of 81.3% [11]. These results indicate that cerebral infarction patients with increased blood glucose levels should have glucose levels measured several times after the acute phase of the disease. Alternatively, these patients should undergo an oral glucose tolerance test to detect previously

undiagnosed diabetes and receive immediate intervention treatment, thereby preventing further exacerbation of the disease and its complications.

Sustained stress hyperglycemia can increase the mortality rate of ischemic stroke patients (especially non-diabetic patients) within 28 days of hospitalization [12]. Elevation of fasting blood glucose and 2 h postprandial glucose levels in patients without diabetes correlates with an increased mortality rate after ischemic stroke. While fasting blood glucose levels are more predictive in females, 2 h postprandial glucose levels are better indicators in male patients [13]. The Glycemia in Acute Stroke (GLIAS) study showed that quick measurement of capillary blood glucose levels within 48 h of stroke ≥ 8.6 mmol/L can predict blood glucose levels after hospitalization and poor prognosis within 3 months [14]. Such prediction is not influenced by age, diabetes, severity of the stroke, or the cerebral infarction area. Thus, the blood glucose levels should be monitored early in patients with elevated blood glucose levels whether or not diabetes is present. Also, interventions to reduce glucose should be utilized to decrease levels to normal and to decrease the risk of a lengthy hospitalization, relapse, and mortality.

An abnormal blood lipid level is a common cause of cerebral infarction. Increased LDL-C is one of the risk factors for atherosclerosis. Control of blood lipids is the primary prevention for cerebrovascular diseases. In the current study we showed that nearly one-half of the cerebral infarction patients have abnormal blood lipid levels. Simultaneous increases in LDL-C, TC, and blood glucose levels are an important risk factor for increased mortality in cerebral infarction patients. The influence of blood glucose levels may explain why abnormal levels of blood lipids alone do not have a significant relationship with the rates of relapse and mortality in cerebral infarction patients. For this reason, lower fasting blood glucose levels will not only decrease the damage caused by hyperglycemia, but will ameliorate the damage due to hyperlipidemia.

Hypertension is an important risk factor for stroke, especially in people who have had hypertension for > 10 years. Control of hypertension is crucial to prevent the development and occurrence of stroke. As part of the body's response to stroke, cerebral infarction patients will experience an increase in blood pressure during the acute phase due to filling of the urinary bladder, pain, compensatory mechanisms to anoxia in the brain, and elevated intracranial pressure. In this study, 64.89% of the patients had hypertension. Cerebral infarction patients with hyperglycemia and an abnormally high or low DBP have an increased mortality rate for the following reasons: (1) DBP is one of the best predictors for fatal stroke in people with hypertension. With every incremental increase in DBP of 1 mmHg, the risk of fatal stroke increases 2.31-fold. (2) Low DBP leads to insufficient blood flow in the brain and further increases ischemic damages. (3) A decrease in DBP may further increase pulse pressure, which is closely associated with mortality rates of stroke patients. (4) Hyperglycemia may exacerbate damage to the brain blood vessels caused by changes in blood pressure. For these reasons, cerebral infarction patients should be cautioned about treatments to lower blood pressure when in the acute phase of the disease.

Taken together, cerebral patients often have elevated fasting blood glucose levels. Hyperglycemia can increase brain damage via multiple mechanisms, increase the length of the hospital stay, increase the rates of relapse and mortality, and adversely affect prognosis. Moreover, hyperglycemia may exacerbate damage to brain blood vessels caused by changes in blood lipids and blood pressure. Therefore, to alleviate the negative effects caused by hyperglycemia, physicians should not only screen for diabetes during the early stage of cerebral infarction, but also initiate glucose-reducing interventions as early as possible.

Disclosure of conflict of interest

None.

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