Impact of Elevated Hemoglobin A1c Levels on Functional Outcome in Patients with Acute Ischemic Stroke

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Background: The association between hemoglobin A1c (HbA1c) and clinical outcomes of acute ischemic stroke is uncertain. We aimed to evaluate the association between initial hemoglobin A1c level and clinical outcome after acute ischemic stroke.

Methods: A total of 408 patients with first-ever acute ischemic stroke were included in this study. We divided the patients into three groups according to HbA1c level: low HbA1c level (HbA1c <5.7%), moderate HbA1c level (HbA1c 5.7-6.4%), and high HbA1c level (HbA1c ≥6.5%). Poor neurological outcomes were defined as modified Rankin Scale (mRS) score of 2-6 at 3 months after stroke. The relation between HbA1c value and clinical outcomes were evaluated by using multivariate logistic regression analyses.

Results: Moderate HbA1c level was present in 126 (30.9%) patients and high HbA1c level in 129 (31.6%) patients. After adjustment for potential confounding variables, both patients in the high HbA1c level group (adjusted odds ratio [OR]: 2.387; 95% confidence interval [CI], 1.201-4.745; $P = .013$) and moderate HbA1c level group (adjusted OR: 1.797; 95% CI, 1.005-3.214; $P = .048$) had a significantly higher poor neurological outcomes than the group in the low HbA1c level. When separately analyzed according to with or without diabetes, the HbA1c level as continuous variable was also associated with poor functional outcome at 3 months in the diabetic patients (adjusted OR: 1.482, 95% CI, 1.013-2.167, $P = .042$), nor in nondiabetic group.

Conclusions: Higher HbA1c on admission was an independent predictor of adverse functional outcome in ischemic stroke patients. Based on this point, tight glycemic control must be necessary for high-risk diabetic patients.

Key Words: Ischemic stroke—hemoglobin A1c—prognosis—hyperglycemia.

Introduction

Acute ischemic stroke is one of the most important causes of human disability and death. Hyperglycemia on admission is frequently present in acute ischemic stroke patients.[1] Acute hyperglycemia is associated with the stress response of ischemic stroke, which may result in poor functional outcome.[2] Admission hyperglycemia is also an independent predictor of poststroke infection in nondiabetic patients[3]. The mechanism of acute hyperglycemia associated with adverse outcome is the exacerbated of the pro-oxidative state, the procoagulant state and the infarction volume.[4,5] However, it is still unclear whether abnormal glucose metabolism is the cause of the worse outcome.

Previous glucose control (PGC) or chronic hyperglycemia, usually defined by hemoglobin A1c (HbA1c), is a marker for average glycemia levels over the past 2-3 months.[6,7] Elevated HbA1c level is associated with high risk of cardiovascular diseases and mortality.[8,9] It has been observed that chronic hyperglycemia prior to stroke is a significant independent predictor of poor functional outcomes,[10] but it is not confirmed in another study.[11]

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However, the association between HbA1c level and clinical outcome in acute stroke patients is still inconsistent.[7,10,12] And there are limited studies about the correlation between HbA1c and long-term outcomes in ischemic stroke patients.

The objective of the present study was to determine whether HbA1c value was associated with functional outcome after acute ischemic stroke.

Methods

Patients

From January 2013 to June 2015, 496 first-ever acute ischemic stroke patients were consecutively enrolled in this hospital-based observational study, which was conducted in the Department of Neurology at the First Affiliated Hospital of Wenzhou Medical University. All patients diagnosed with acute ischemic stroke were confirmed by clinical symptoms and neuroimages according to the recommendations from World Health Organization.[13] In this study, we included patients admitted within 72 hours of ischemic stroke. The present study was approved by the ethics committee of the First Affiliated Hospital of Wenzhou Medical University. All patients or their relatives gave signed informed consent in this study.

Clinical Assessment

Baseline information was collected about age, sex, medical history, medications, and detailed demographics data within 24 hours of admission. The severity of neurological impairment was assessed by the National Institutes of Health Stroke Scale (NIHSS) on the first day after admission. Admission blood glucose was measured in the emergency room. HbA1c levels and other blood biochemical variables were routinely measured within 24 hours after hospital admission from fasting patients in the morning. Stroke subtypes were classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) study.[14]

Hypertension was defined as at least 2 raised blood pressure level ≥140/90 mmHg or use of antihypertensive medicines. Diabetes was diagnosed as use of antidiabetic medicines, previous physician diagnosis, or HbA1c ≥6.5%. Dyslipidemia was diagnosed as total cholesterol level >6.21 mmol/L, serum triglyceride concentration >2.26 mmol/L, or use of cholesterol-lowering agents. Atrial fibrillation was defined according to medical records or conclusive electrocardiogram data. Smoking habits was defined as patients who had smoked at least 1 cigarette/d for >6 months. On the basis of American Diabetes Association's Standards of Care,[15] we divided the patients into three groups according to HbA1c level: (a) the high HbA1c level (HbA1c ≥6.5 %), (b) the moderate HbA1c level (HbA1c 5.7-6.4%), and (c) the low HbA1c level (HbA1c <5.7%).

Outcome Measures

The prognosis of all patients was evaluated on the basis of the mRS through outpatient department or telephone follow-up by a trained neurologist. Poor functional outcomes were defined as an mRS score of 2-6 at 3 months after stroke.

Statistical Analyses

Statistical analyses were performed with the SPSS 22.0 package for Windows (SPSS Inc., Chicago, IL, RRID: SCR_002865). P value <0.05 were considered to be statistically significant. Continuous variables were expressed as means with standard deviations or medians with interquartile ranges. Categorical variables were expressed as percentages. Statistical analyses were performed using Student's t-test, one-way analysis of variance and Kruskal-Wallis for continuous data, chi-square test or Fisher exact test for categorical data. We compared the difference of characteristics between the poor outcome group and favorable outcome group. We conducted different multivariate logistic regression models to evaluate the association between HbA1c level and poor functional outcomes at 3 months. We also further analyzed the relationship between HbA1c level and functional outcome in diabetes group and non-diabetes group respectively, and additional logistical regression analyses were performed.

Results

Among a total of 496 patients, 55 patients with admission after 72 hours of onset were excluded. In the rest of the patients, 16 patients with no data on HbA1c and 17 patients who were lost to follow-up were also excluded. Finally, we enrolled 408 patients in this study (Fig 1).

At baseline, the mean age of all patients was 63.8 ± 11.5 years old, and 261 patients (64.0%) were male. The median NIHSS score was 5. The mean HbA1c level was 6.4 ± 1.5 mmol/L with a range of 3.7-14.9 mmol/L, and 147 patients (36.0%) including known pre-existent (n = 91) and newly (n = 56) were diagnosed as diabetes. Moderate HbA1c level was present in 126 (30.9%) patients and high HbA1c level in 129 (31.6%) patients. 117 patients (28.7%) were treated with intravenous rtPA. Poor neurological outcome at third month was present in 196 (48.0%) patients. Baseline characteristics for the whole study participants and clinical characteristics stratified for HbA1c level were presented in Table 1.

Patients with moderate HbA1c level were significantly older than those with high HbA1c level. Diabetes and dyslipidemia were more frequent in the high HbA1c level group than the low HbA1c level group. NIHSS at admission did not differ between these three groups (P = .821). Moreover, patients with high HbA1c level were significantly associated with higher admission glucose level, lower high-density lipoprotein cholesterol level, and

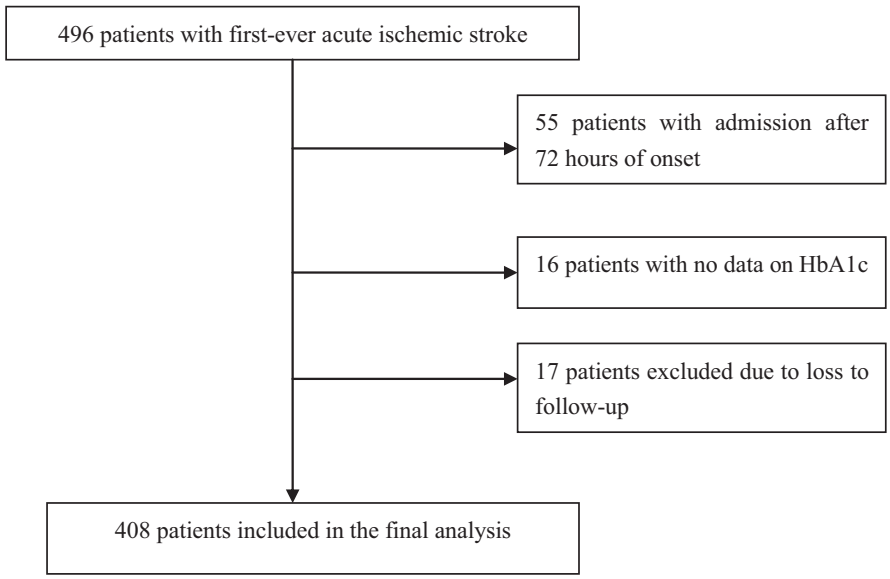

Figure 1. *Flow diagram showing the patient selection.*

Table 1. *Baseline characteristics and clinical characteristics stratified for HbA1c level*

Variables	All patients ($n = 408$)	Tertiles of HbA1c, mmol/L			*P* Value
		Low HbA1c level ($n = 153$)	Moderate HbA1c level ($n = 126$)	High HbA1c level ($n = 129$)	
Age, years, mean ± SD	63.8 ± 11.5	63.1 ± 13.2	65.9 ± 10.7	62.7 ± 9.8	.051
Male sex, *n* (%)	261 (64.0)	91 (59.5)	85 (67.5)	85 (65.9)	.331
HbA1c, mmol/L, mean ± SD	6.4 ± 1.5	5.3 ± 0.3	5.9 ±0.2	8.1 ± 1.5	<.001
Comorbidities, *n* (%)					
Hypertension	306(75.0)	109 (71.2)	93 (73.8)	104 (80.6)	.181
Diabetes	147 (36.0)	3 (2.0)	15 (11.9)	129 (100)	<.001
Dyslipidemia	131 (32.1)	34 (22.2)	43 (34.1)	54 (41.9)	.002
Atrial fibrillation	53 (13.0)	19 (12.4)	20 (15.9)	14 (10.9)	.474
Smoking, *n* (%)	161 (39.5)	61 (39.9)	49 (38.9)	51 (39.5)	.986
NIHSS at admission, median (IQR)	5 (3-8)	4 (3-8)	5 (2-8)	5 (3-8)	.821
Laboratory findings, mmol/L, mean ± SD					
Admission glucose	8.3 ± 3.7	6.6 ± 1.5	7.1 ± 1.7	11.5 ± 4.7	<.001
Total cholesterol	5.0 ± 1.2	4.9 ± 1.1	5.0 ± 1.2	5.0 ± 1.3	.460
Triglycerides	1.7 ± 1.0	1.4 ± 0.6	1.7 ± 1.1	2.1 ± 1.2	<.001
HDL-C	1.1 ± 0.3	1.2 ± 0.3	1.1± ± 0.3	1.1 ± 0.3	.006
LDL-C	3.0 ± 0.9	3.0 ± 0.9	3.0 ± 0.9	3.0 ± 1.0	.765
Uric acid	305.6 ± 101.6	303.4v110.3	316.9 ± 86.8	297.4 ± 103.7	.297
Blood albumin	38.8 ± 3.9	39.0 ± 3.9	38.7v4.0	38.7±3.8	.801
Systolic BP, mmHg, mean ± SD	155.9 ± 23.6	154.9 ± 24.0	154.6 ± 22.4	158.4 ± 24.2	.349
Diastolic BP, mmHg, mean ± SD	85.4 ± 15.2	85.8 ± 17.2	84.9 ± 13.7	85.3 ± 14.0	.874
Intravenous rtPA, *n* (%)	117 (28.7)	37 (24.2)	4 5(35.7)	35 (27.1)	.095
Stroke subtype, *n* (%)					.470
Large artery atherosclerosis	237 (58.1)	85 (55.6)	71 (56.3)	81 (62.8)	
Small artery occlusion	71 (17.4)	31 (20.3)	21 (16.7)	19 (14.7)	
Cardioembolism	30 (7.4)	13 (8.5)	6 (4.8)	11 (8.5)	
Other determined etiology	8 (2.0)	4 (2.6)	3 (2.4)	1 (0.8)	
Undetermined cause	62 (15.2)	20 (13.1)	25 (19.8)	17 (13.2)	

Abbreviations: HbA1c, hemoglobin A1c; NIHSS, National Institute of Health stroke scale; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BP, blood pressure; rtPA, recombinant tissue plasminogen activator; SD, standard deviation; IQR, interquartile range.

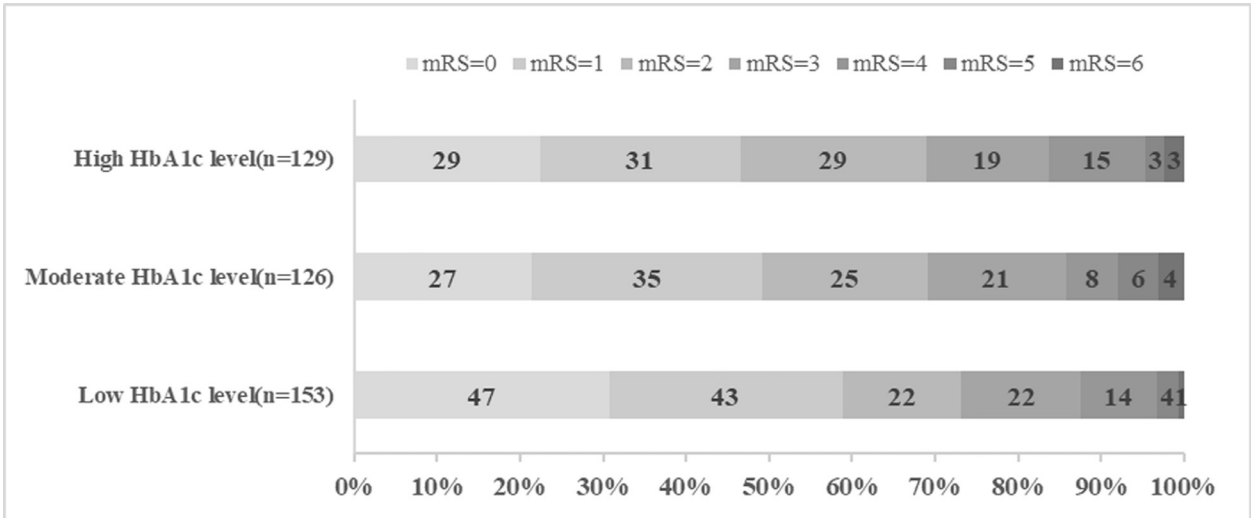

Figure 2. *Functional outcome at 3 months stratified for HbA1c level.*

higher triglycerides level. There were no statistically significant difference among the groups with regard to sex, smoking, hypertension, atrial fibrillation, and stroke subtypes. The distribution of functional outcome at 3 months stratified for three HbA1c levels is shown in Figure 2. The trendence of significant differences between the three groups were perceived in regard to 3-month poor outcomes ($\chi^2 = 4.804$, $P = .091$). The comparison of baseline characteristics and functional outcome between each stroke subtypes is presented in Table 2. The prognosis of large artery atherosclerosis group is poorer than the small artery occlusion group.

Table 3 shows the characteristics compared between patients with poor and favorable outcome. The patients with poor outcome were older, had higher NIHSS score, HbA1c level and diabetes rates than patients with favorable outcome.

Table 4 shows the association between HbA1c level and poor outcome. After adjustment for Model 1 plus variables such as admission glucose, triglycerides and blood albumin that were identified as P value <0.2 in the Table 3, the clinical outcome decreased substantially as HbA1c value became higher. These findings were still existed after adjustment for Model 2 plus stroke subtype, hypertension, atrial fibrillation, smoking, uric acid, systolic BP, and diastolic BP, patients in the high HbA1c level group and the moderate HbA1c level group had a significantly higher risk of poor functional outcome at 3 months than the group in low HbA1c level (Model 3; $P = .013$, and $P = .048$). Subgroup multivariate logistic regression analyses were respectively conducted in the diabetic patients and nondiabetic patients. Taking the HbA1c as continuous variable, we found that HbA1c was a significant predictor of poor functional outcome at 3 months in diabetic patients (Model 3; $P = .042$). Nevertheless, in nondiabetic group, HbA1c was not associated with a risk of poor functional outcome in model 3 ($P = .475$). We also found that, in large artery atherosclerosis group, increasing HbA1c level (OR 1.396, 95% CI 1.022-1.908, $P = .036$) was independently associated with a higher risk of poor functional

Table 2. *Baseline characteristics and functional outcome according to stroke subtypes*

	Large artery atherosclerosis ($n = 237$)	Small artery occlusion ($n = 71$)	Cardioembolism ($n = 30$)	Other determined etiology ($n = 8$)	Undetermined cause ($n = 62$)	*P*
Age, mean ± SD, years	64.5 ± 10.7	60.4 ± 11.1	67.8 ± 12.7	55.9 ± 13.6	64.4v13.1	.006
Male sex, *n* (%)	151 (63.7)	42 (59.2)	20 (66.7)	5 (62.5)	43 (69.4)	.808
HbA1c, mmol/L, mean ± SD	6.6 ± 1.6	6.2 ± 1.4	6.3 ± 1.2	6.0 ± 0.8	6.2 ± 1.0	.147
NIHSS at admission, median (IQR)	5 (3-7)	3 (2-6)	9 (3-11)	4.5 (2.5-5)	7 (3.5-10)	.000
Intravenous rtPA, *n* (%)	51 (21.5)	15 (21.1)	16 (53.3)	5 (62.5)	30 (48.4)	.000
mRS2-6, *n* (%)	125(52.7)	24 (33.8)	15 (50)	1 (12.5)	31 (50)	.017

Abbreviations: HbA1c, hemoglobin A1c; mRS, modified Rankin Scale; NIHSS, National Institute of Health stroke scale; rtPA, recombinant tissue plasminogen activator.

Table 3. *Comparison of the risk factors between patients with poor and favorable outcome*

Variables	Poor outcome ($n = 196$)	Favorable outcome ($n = 212$)	P value
Age, mean ± SD, years	65.5 ± 11.2	62.3 ±11.6	.006
Male sex, *n* (%)	125 (63.8)	136 (64.2)	.937
HbA1c level (tertiles), *n* (%)			
<5.7	63 (32.1)	90 (42.5)	
5.7-6.4	64 (32.7)	62 (29.2)	
≥6.5	69 (35.2)	60 (28.3)	.091
HbA1c,mmol/L, mean ± SD	6.6 ± 1.6	6.2 ± 1.3	.018
Comorbidities, *n* (%)			
Hypertension	151 (77.0)	155 (73.1)	.360
Diabetes	81 (41.3)	66 (31.1)	.032
Dyslipidemia	57 (29.1)	74 (34.9)	.208
Atrial fibrillation	26 (13.3)	27 (12.7)	.874
Smoking, *n* (%)	83 (42.3)	78 (36.8)	.251
NIHSS at admission, median (IQR)	7 (4-10)	3 (2-6)	<.001
Laboratory findings, mmol/L, mean ± SD			
Admission glucose	8.5 ± 3.6	8.0 ± 3.8	.178
Total cholesterol	4.9 ± 1.1	5.0 ± 1.2	.435
Triglycerides	1.6 ± 0.8	1.8 ± 1.2	.145
HDL-C	1.1 ± 0.3	1.1 ± 0.3	.295
LDL-C	3.0 ± 1.0	3.0 ± 0.9	.964
Uric acid	300.8 ± 93.7	310.1 ± 108.4	.356
Blood albumin	38.5 ± 3.8	39.1 ± 3.9	.150
Systolic BP (mmHg)	156.8 ± 23.4	155.1 ± 23.7	.484
Diastolic BP (mmHg)	85.3 ± 15.5	85.4 ± 14.9	.935
Intravenous rtPA, *n* (%)	52 (26.5)	65 (30.7)	.357

Abbreviations: BP, blood pressure; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; NIHSS, National Institute of Health stroke scale; rtPA, recombinant tissue plasminogen activator; SD, standard deviation.

outcome after adjustment for Model 3 except stroke subtype.

Discussion

Our study showed that functional independence in patients with ischemic stroke decreased with increasing HbA1c level on admission. Although patients with higher HbA1c level had more adverse risk factors than the lower HbA1c level cases in our study, the association between an elevated HbA1c level and poor outcome was still persisted after adjusting for risk factors as mentioned above.

It was well proven that acute hyperglycemia adversely affects short and long-term outcome after ischemic stroke.[1,2,16,17] In our study, we found no association between admission blood glucose and functional outcome. One account for this difference is that most patients in our study had mild stroke severity. And hyperglycemia is just associated with severe stroke.[2] Another explanation for the discrepancy is that the patients have more proportion of diabetes in our study. A systematic review indicated that acute hyperglycemia has no effect on clinical outcome in diabetic patients.[1] Admission glucose level was not a marker of mortality in diabetes mellitus patients who was in poor previous glucose control.[7] However, little study allowed to evaluate the possible role of acute blood glucose level in the relation between HbA1c and poor outcome. Admission hyperglycemia did not attenuate the risk of poor outcome associated with HbA1c.[10,18] But some studies found no association between prestroke glycemic control and unfavorable outcome after adjusting for fasting glucose.[10] In our study, the association was still confirmed after adjusting for admission glucose.

The relationship between HbA1c level and outcome after acute ischemic stroke is controversial. The study included only 99 participants indicate that prestroke hyperglycemia did not have any effect on functional outcome.[19] A study with large sample size of ischemic stroke patients showed no relationship between HbA1c level and mortality at 3 months.[7] However, the other studies suggested that poor prestroke glycemic control had a deleterious effect on clinical outcome,[10,18,20] which is in line with the results from our study. Furthermore, the inverse impact of chronic hyperglycemia on functional outcome was only acquired in the subgroup of diabetic patients in our cohort, nor in nondiabetic patients. Roquer et al reported that HbA1c value was not associated with 3-month mortality in presence/absence in diabetic patients.[7] Another study presented that increasing HbA1c level is detrimental to functional outcomes in

Table 4. *Odds ratios for poor functional outcome according to HbA1c level*

	Multivariate adjusted (model 1)		*P*	Multivariate adjusted (model 2)		*P*	Multivariate adjusted (model 3)		*P*
	OR	95% CI		OR	95% CI		OR	95% CI	
All patients									
HbA1c level (tertiles)									
Low HbA1c level	Ref								
Moderate HbA1c level	1.608	0.924-2.800	.093	1.796	1.017-3.171	.044	1.797	1.005-3.214	.048
High HbA1c level	1.951	1.133-3.360	.016	2.261	1.153-4.430	.018	2.387	1.201-4.745	.013
HbA1c as continuous variable	1.207	1.031-1.413	.019	1.369	1.074-1.744	.011	1.386	1.081-1.777	.010
Diabetic patients ($n = 147$)									
HbA1c as continuous variable	1.130	0.880-1.452	.338	1.245	0.903-1.714	.181	1.482	1.013-2.167	.042
Nondiabetic patients ($n = 261$)									
HbA1c as continuous variable	1.233	0.581-2.620	.585	1.495	0.671-3.330	.325	1.355	0.589-3.118	.475

Model 1 = adjusted for age, sex, intravenous rtPA, National Institutes of Health Stroke Scale score.
Model 2 = adjusted for Model 1 plus variables such as admission glucose, triglycerides and blood albumin that were identified as *P* value<.2 in the Table 3.
Model 3 = Model 2 plus stroke subtype, hypertension, atrial fibrillation, smoking, uric acid, systolic BP and diastolic BP.
Abbreviations: CI, confidence interval; HbA1c, hemoglobin A1c; OR, odds ratio.

both diabetics and non-diabetic patients, but not in whole patients.[12]

Several potential mechanisms are proposed to explain why elevated HbA1c have predictive value for poor outcome of ischemic stroke. First, persistent hyperglycemia may enlarge the infarction volume and result in worse outcome.[4] Second, chronic hyperglycemia has been linked to cerebral tissue and cerebral vasculature changes, such as white matter hyperintensity[21] and smaller lacunes,[22] which may predispose to poor outcome. Third, hyperglycemia can induce a pro-oxidative state and result in direct neuronal toxicity.[5] Oxidative stress and elevated coagulation factors caused by chronic hyperglycemia may lead to a prothrombotic shift.[23] And these factors can be interrelated, and aggravate the brain damage.

However, the effect of glucose-lowering treatment on clinical outcome after ischemic stroke is not being confirmed in randomized-controlled trials.[24] Our study provides powerful evidence that prestroke glycemic control may influence the clinical course and outcome of ischemic stroke. The current study had certain limitations. First of all, HbA1c level and follow-up data were not available in thirty-three patients included in the study. But there were no significant differences of the baseline characteristics between the excluded patients and included patients. Second, this analysis was carried out in a single hospital, which may not be generalized to all other stroke patients. In addition, another point is that a single HbA1c evaluation on admission, result in underestimating long-term glycemia after ischemic stroke linked to 3-month outcome.

Conclusion

In brief, our study presents some remarkable observations. First, HbA1c determination after ischemic stroke was useful for identifying undiagnosed diabetes. Second, higher HbA1c level on admission was an independent predictor of adverse functional outcome in ischemic stroke patients, and this association did not attenuate after adjustment for initial blood glucose. Third, in subgroup analysis, chronic hyperglycemia was also associated with poor clinical outcome in diabetic patients. Based on these points, tight glycemic control must be necessary for high-risk diabetic patients.

References

1. Capes SE, Hunt D, Malmberg K, et al. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. Stroke 2001;32:2426-2432.
2. Tziomalos K, Dimitriou P, Bouziana SD, et al. Stress hyperglycemia and acute ischemic stroke in-hospital outcome. Metabolism 2017;67:99-105.
3. Zonneveld TP, Nederkoorn PJ, Westendorp WF, et al. Hyperglycemia predicts poststroke infections in acute ischemic stroke. Neurology 2017;88:1415-1421.

4. Baird TA, Parsons MW, Phan T, et al. Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. Stroke 2003;34:2208-2214.
5. Garg R, Chaudhuri A, Munschauer F, et al. Hyperglycemia, insulin, and acute ischemic stroke: A mechanistic justification for a trial of insulin infusion therapy. Stroke 2006;37:267-273.
6. Goldstein DE, Little RR, Lorenz RA, et al. Tests of glycemia in diabetes. Diabetes Care 2004;27(Suppl 1):S91-S93.
7. Roquer J, Giralt-Steinhauer E, Cerda G, et al. Glycated hemoglobin value combined with initial glucose levels for evaluating mortality risk in patients with ischemic stroke. Cerebrovasc Dis 2015;40:244-250.
8. Khaw KT, Wareham N, Bingham S, et al. Association of hemoglobin a1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. Ann Intern Med 2004;141:413-420.
9. Drechsler C, Krane V, Ritz E, et al. Glycemic control and cardiovascular events in diabetic hemodialysis patients. Circulation 2009;120:2421-2428.
10. Luitse MJ, Velthuis BK, Kappelle LJ, et al. Chronic hyperglycemia is related to poor functional outcome after acute ischemic stroke. Int J Stroke 2017;12:180-186.
11. Sung JY, Chen CI, Hsieh YC, et al. Comparison of admission random glucose, fasting glucose, and glycated hemoglobin in predicting the neurological outcome of acute ischemic stroke: a retrospective study. PeerJ 2017;5:e2948.
12. Lei C, Wu B, Liu M, et al. Association between hemoglobin a(1)c levels and clinical outcome in ischemic stroke patients with or without diabetes. J Clin Neurosci 2015;22:498-503.
13. Stroke—1989. Recommendations on stroke prevention, diagnosis, and therapy. Report of the who task force on stroke and other cerebrovascular disorders. Stroke 1989;20:1407-1431.
14. Adams Jr. HP, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. Toast. Trial of org 10172 in acute stroke treatment. Stroke 1993;24:35-41.
15. American Diabetes A.. Standards of medical care in diabetes—2014. Diabetes Care 2014;37(Suppl 1):S14-S80.
16. Luitse MJ, Biessels GJ, Rutten GE, et al. Diabetes, hyperglycaemia, and acute ischaemic stroke. Lancet Neurol 2012;11:261-271.
17. Yao M, Ni J, Zhou L, et al. Elevated fasting blood glucose is predictive of poor outcome in non-diabetic stroke patients: a sub-group analysis of smart. PLoS One 2016;11:e0160674.
18. Kamouchi M, Matsuki T, Hata J, et al. Prestroke glycemic control is associated with the functional outcome in acute ischemic stroke: the fukuoka stroke registry. Stroke 2011;42:2788-2794.
19. Murros K, Fogelholm R, Kettunen S, et al. Blood glucose, glycosylated haemoglobin, and outcome of ischemic brain infarction. J Neurol Sci 1992;111:59-64.
20. Gao Y, Jiang L, Wang H, et al. Association between elevated hemoglobin a1c levels and the outcomes of patients with small-artery occlusion: a hospital-based study. PLoS One 2016;11:e0160223.
21. Tamura Y, Araki A. Diabetes mellitus and white matter hyperintensity. Geriatr Gerontol Int 2015;15(Suppl 1):34-42.
22. Bezerra DC, Sharrett AR, Matsushita K, et al. Risk factors for lacune subtypes in the atherosclerosis risk in communities (aric) study. Neurology 2012;78:102-108.
23. Lemkes BA, Hermanides J, Devries JH, et al. Hyperglycemia: A prothrombotic factor. J Thromb Haemost 2010;8:1663-1669.
24. Bellolio MF, Gilmore RM, Stead LG. Insulin for glycaemic control in acute ischaemic stroke. Cochrane Database Syst Rev 2011. CD005346.