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Association of HbA1c Levels with Extent and Functional Status of Ischemic and Hemorrhagic Stroke

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Abstract

Background: HbA1c is an established diagnostic index which is used to assess diabetes mellitus. The aim of this study was to evaluate the association between HbA1c level with the types of stroke as well as the extent and functional status of ischemic stroke (IS) and hemorrhagic stroke (HS) in patients.

Methods: In this cross-sectional study, we evaluated 120 patients with IS and HS. The functional outcome was evaluated based on the MRS criteria. The extent of the lesion was determined according to CT scan and MRI. We measured the blood hemoglobin A1c (HbA1c) levels in all patients after stroke.

Results: HbA1c level in the IS group was significantly higher compared to the HS group ($p < 0.05$). There was a statistically significant difference between the extent of the lesion and the functional status of patients with the type of stroke ($P < 0.001$). History of smoking, in the IS group, was significantly associated with exposure to worse functional outcome ($p<0.05$). In the HS group, there was a significant relationship between hyperlipidemia histories with worse functional outcome. However, the relationship between HbA1c level and MRS score was inversely significant ($p<0.05$). Data analysis showed that, only in the IS group, the relationship between some independent variables, history of HLP and smoking, and the extent of stroke was significant ($p<0.05$).

Conclusion: Findings of this study showed that there was a significant association between HbA1c levels as well as the extent and functional status with the type of stroke. There was a significant inverse relationship between HbA1c levels with the MRS score.

Introduction

Stroke is a leading cause of disability and death worldwide, affecting almost 800,000 people in the United States each year (1). About 87% of strokes are ischemic (IS), in which blood flow to the brain is reduced; the remaining 13% are hemorrhagic (HS), in which a vessel ruptures and blood accumulates in the brain (2). There are several risk factors that can lead to stroke, including diabetes mellitus (DM), hypertension (HTN), smoking, and dyslipidemia (3). It has been shown that patients with type 1 and 2 diabetes mellitus have a markedly increased risk of stroke compared to the non-diabetic subjects (4, 5). Stroke risk in individuals with diabetes is at least twice more compared to the non-diabetic subjects and approximately 20% of diabetic patients will die from stroke (6). In addition, it has been reported that the prevalence of DM in patients with IS is 15% to 44% (7). The initial causes of ischemic stroke in diabetes mellitus patients include cerebrovascular atherosclerosis and thrombosis (8). Hemoglobin A1c (HbA1c) is an index for evaluating the glucose level at an intermediate term. Also, it reflects the average levels of serum glucose for 2 to 3 months (5). Therefore, HbA1c level can be used to accurately predict the risk for diabetes in subjects (9). The normal range for HbA1c is less than 6%, but it exceeds 6% in the patients with diabetes and can increase up to 10%–12% (10). Some studies evaluated the value of HbA1c determination during acute IS in large and small series of patients (7, 11, 12). Robson et al. reported that the level of HbA1c was 0.4% higher before their stroke compared to the control group (13). Despite evidences for a positive association between increased HbA1c levels and duration of diabetes with risk of IS among patients with diabetes, but there are a few studies on the relationship of HbA1c levels with extent and functional status of ischemic and hemorrhagic stroke. Thus, the aim of this study was to investigate the association between HbA1c levels with the types of stroke as well as the extent and functional state of IS and HS in patients hospitalized in the neurology ward of Ali-Ibn Abi Talib hospital in Rafsanjan, Iran.

Materials and Methods

In the present study, 120 patients with IS (n = 95) and HS (n = 25) were included. This study is a cross-sectional evaluation of patients with IS and HS that were referred to the neurology ward of Ali-Ibn Abi-Talib hospital in Rafsanjan, Iran. The period of this study was one year and the number of patients admitted during this period was 128 subjects (8 patients were excluded). Patients entered the study based on census method. Patients received information about a clinical study as an informed consent. Diagnosis of disease was performed based on clinical examination and imaging techniques such as computerized tomography (CT) scan and magnetic resonance imaging (MRI). Data were collected by observation, examination and also serum HbA1c levels were measured by the biochemical methods.

The functional status was evaluated by MRS questionnaire, a criteria to determine the functional outcome of disease from no symptom (G0) to severe disability (G5) and death (G6). The extent of the lesions was evaluated according to CT scan and MRI techniques. Patients with IS were classified into Lacunar, Minor and Major. The Major type was considered as a stroke with a size more than one-third of the middle cerebral artery (MCA) territory. The lacunar lesion was considered as a stroke with a size less than 20 millimeters in diameter. If the size was between Major and Lacunar, then it was considered as Minor. In hemorrhagic strokes, there were three types of sizes. The Minor lesions were considered as hematoma with a diameter less than 20 millimeters, the Major had a diameter more than 40 millimeters and the Medium was between major and minor. Diabetes, HTN and dyslipidemia were defined as Fasting plasma glucose ≥ 126 mg/dl (≥ 7.0 mmol/dl) (14), blood pressure higher than 140 over 90 millimeters of mercury (mmHg) (15) and Hypercholesterolemia: fasting total cholesterol ≥240 mg/dL or Hypertriglyceridemia: fasting serum triglyceride level ≥ 200 mg/dL (16) along with the history of taking anti-diabetes, anti-hypertensive or anti-dyslipidemia drugs respectively. Smokers were those who responded "yes" to smoking in the year prior to admission and had pack years not equal to 0 (17).

Spectrophotometer was used to measure the blood level of HbA1c. After RBC lysis induction using solution reagents, automatic analyses were conducted to measure light absorption by releasing H5B, and the amount of HbA1c was determined by calculating the difference between the absorbance at 660 and 800 nm.

Statistical analysis

Demographic characteristics of patients and laboratory examination data are presented as number (%), and also the age and blood level of HbA1c data are expressed as mean ± SD. We analyzed age and HbA1c level data using independent t-test in ischemic and hemorrhagic stroke groups. Chi-square test for other variables was used as data were not continuous variables. Ordinal and multinomial logistic regression analysis was applied to compare the odds ratio (OR) of patients with ischemic and hemorrhagic stroke after adjusting for other variables in each group. All statistical assessments were two-tailed and a value of $P<0.05$ was considered significant. All data were analyzed using SPSS statistical software (version 21, Chicago, IL, USA).

Results

In this study, 120 patients of total stroke cases were studied. Out of these, 95 patients (79.2%) were in IS group and 25 patients (20.8%) were in HS group. Baseline characteristics of the patients are shown in Table 1. As shown in this table, there was no statistically significant difference in the age of patients with IS and HS ($p= 0.884$). The highest frequency in both types of strokes was observed in women but there was no statistically significant relationship between sex and type of stroke ($p= 0.313$). The level of HbA1c in the IS group was significantly higher compared to the HS group ($p = 0.032$). The extent of the lesions in the majority of patients with HS (60%) was a major type while the extent of injury was minor in most patients with IS (43.2%). Therefore, there was a statistically significant difference between the extent of the lesion and the type of stroke ($p=0.001$). There was a history of hypertension in 88% of patients with HS, while this ratio for IS patients was only 57.9% ($p = 0.005$). The highest prevalence (72%) in the patients with HS, based on the functional status (MRS score), was in Grade 5 and 6 while 21% of patients with IS were in Grade 5 and in Grade 6. Therefore, there was a significant difference between the type and functional status of stroke ($p=0.001$). There was no statistically significant relationship between diabetes, hyperlipidemia (HLP) and smoking history with the types of stroke ($p>0.05$).

Table 1. Demographic and physical/clinical variables of patients with ischemic and hemorrhagic stroke

Variables	Ischemic stroke (IS)	Hemorrhagic stroke (HS)	P
Mean age, years (SD)	72.15 (12.1)	71.6 (12.9)	0.844
Gender			0.313
Male (%)	41 (43.2)	8 (32.0)	
Female (%)	54 (56.8)	17 (68.0)	
Extent (%)			0.001*
Minor	41 (43.2)	5 (20)	
Medium	-	5 (20)	
Major	27 (28.4)	15 (60)	
Lacunar	27 (28.4)	-	
Mean blood HbA1C, (SD)	6.44 (1.79)	5.78 (1.19)	0.032*
Non-diabetic (<5.7%)	52 (54.7)	16 (64.0)	0.406
Diabetic (≥5.7%)	43 (45.3)	9 (36.0)	
Previous hypertension (%)	55 (57.9)	22 (88.0)	0.005*
Previous HLP (%)	35 (36.8)	8 (32.0)	0.635
Previous smoking (%)	25 (26.3)	9 (36.0)	0.339
Functional status / MRS score (%)			
G0	0 (0)	0 (0)	
G1	21 (22.1)	0 (0)	
G2	21 (22.1)	2 (8.0)	0.001*
G3	12 (12.6)	3 (12.0)	
G4	21 (22.1)	2 (8.0)	
G5	20 (21.1)	16 (64.0)	
G6	0 (0)	2 (8.0)	

Data were presented as number (%) except for mean ± SD for age and HbA1c. Data between two groups were compared using independent t-test for age and HbA1c; Pearson chi-square test for other variables. * p<0.05 was significantly different between the two groups.

The results of the univariate and multivariate analysis are presented in table 2. In the univariate analysis, there was no statistically significant relationship between independent variables and the functional status of stroke in each of the two groups (p>0.05). Multivariate analysis showed that the history of smoking in the IS group was significantly associated with exposure to worse functional status (OR 3.29; 95% CI 1.29-8.37, *p*= 0.012). In HS group, there was a significant relationship between the history of HLP with worse functional status as well as a significant inverse relationship between HbA1c levels with this indicator (OR 2.76; 95% CI 1.07-7.07, *p*= 0.034 for history of HLP and OR 0.536; 95% CI 0.30-0.93, *p*= 0.029 for HbA1c level).

Table 2. Comparison of odds ratio (OR) of patients with ischemic and hemorrhagic stroke after adjusting for other variables for each group

Variables (Reference)	Ischemic stroke (IS)			Hemorrhagic stroke (HS)		
	β	OR (95%CI)	Adjusted OR (95%CI)	β	OR (95%CI)	Adjusted OR (95%CI)
Age (year)	0.019	1.01 (0.99-1.04)	1.03 (1.00-1.06)	-0.01	0.99 (0.92-1.05)	1.01 (0.98-1.04)
Gender	0.379	1.46 (0.70-3.04)	2.04 (0.90-4.63)	-2.10	0.12 (0.01-1.28)	0.14 (0.10-2.06)
Blood HbA1C	0.078	1.08 (0.89-1.30)	1.22 (0.89-1.68)	-0.17	0.84 (0.44-1.58)	0.536 (0.30-0.93)
Previous Diabetic	0.139	1.14 (0.55-2.36)	0.87 (0.27-2.76)	0.239	1.27 (0.20-7.86)	5.31 (0.09-2.99)
Previous hypertension	0.066	1.06 (0.51-2.22)	0.85 (0.39-1.85)	0.153	1.16 (0.12-10.5)	2.57 (0.14-4.28)
Previous HLP	-0.09	0.91 (0.43-1.90)	0.83 (0.38-1.80)	1.144	3.14 (0.47-20.6)	2.76 (1.07-7.07)
Previous smoking	0.623	1.86 (0.83-4.14)	3.29 (1.29-8.37)	0.372	1.45 (0.25-8.30)	0.437 (0.18-1.04)

The odds ratio (OR) was presented using ordinal logistic regression analysis. Adjusted odds ratio (OR) was presented after adjusting for other variables for each group. In this analysis, the functional status is a variable response and other variables included in the table are independent variables.

Table 3 shows the results of the univariate and multivariate analysis of patients with ischemic stroke based on diabetes and non-diabetes. There was no statistically significant relationship between independent variables and the functional status of stroke in each of the two groups ($p>0.05$). Conducting the univariate and multivariate analysis of patients with hemorrhagic stroke based on diabetes and non-diabetes was not possible due to the small number of patients in this group.

Table 3. Comparison of odds ratio (OR) of patients with ischemic stroke based on diabetes or non-diabetes after adjusting for other variables for each group

	Ischemic stroke (IS)					
	Diabetic			Non-diabetic		
Variables Reference)	**β**	**OR (95%CI)**	**Adjusted OR (95%CI)**	**B**	**OR (95%CI)**	**Adjusted OR (95%CI)**
Age (year)	0.029	1.02 (0.98-1.07)	1.04 (0.98-1.09)	0.016	1.01 (0.97-1.05)	1.02 (0.98-1.07)
Gender	0.109	1.10 (0.37-3.25)	2.14 (0.53-8.59)	0.624	1.86 (0.68-5.08)	1.98 (0.68-5.76)
Blood HbA1C	0.078	1.11 (0.84-1.48)	1.24 (0.9-1.72)	-0.16	0.84 (0.12-5.85)	0.945 (0.12-7.30)
Previous hypertension	-0.26	0.77 (0.25-2.30)	0.64 (0.19-2.08)	0.324	1.38 (0.51-3.72)	0.966 (0.33-2.77)
Previous hyperlipidemia	-0.91	0.401 (0.13-1.21)	0.35 (0.11-1.14)	0.592	1.80 (0.64-5.03)	1.695 (0.58-4.93)
Previous smoking	0.56	1.75 (0.49-6.19)	4.39 (0.82-9.80)	0.702	2.01 (0.70-5.75)	2.66 (0.82-8.61)

The odds ratio (OR) was presented using ordinal logistic regression analysis. Adjusted odds ratio (OR) was presented after adjusting for other variables for each group. In this analysis, the functional status is a variable response and other variables included in the table are independent variables.

Data analysis using univariate and multivariate models in nominal logistic regression showed (Fig. 1) that in the IS group, only at the level of major response compare to Lacunar, history of HLP and smoking were significant variations (OR 0.171, p= 0.010 for HLP and OR 4.78, p= 0.032 for smoking) while the relationship between independent variables and the different extent levels of stroke in the HS group was not significant.

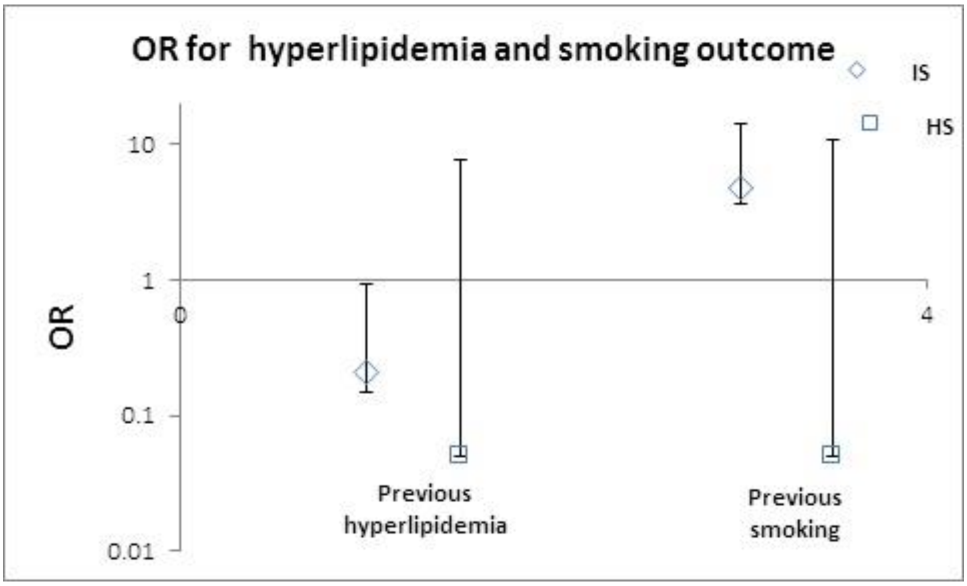

Fig 1. In this analysis, the stroke extent is a variable response and other variables included in the table are independent variables. Adjusted odds ratio (OR) was presented using multinomial logistic regression analysis after adjusting for other variables for each group. Reference level for ischemic and hemorrhagic stroke is respectively Lacunar and Major.

Discussion

In the present study, the association between the HbA1c level (as a criteria for diabetes control) with the type of stroke (IS and HS) as well as the functional status and the extent of them were investigated. Our results showed that the HbA1c level was significantly higher in the IS group compared to the HS group. There was a significant relationship between the extent of the lesion and the functional status with the type of stroke. The extent of the lesion in most patients with HS was Major type and in most patients with IS was Minor type. Eighty eight percent of patients with HS and 57% of patients with IS had a history of hypertension. There was a significant relationship between the histories of smoking, in IS group, as well as hyperlipidemia history, in HS group, with worse functional outcome. The relationship between the HbA1c level and functional status was inversely significant.

Diabetes leads to higher incidence of all-cause death with 1.3 fold increase in adjusted risk among stroke patients (5). It is well established that diabetes mellitus is associated with systemic and intracranial atherosclerotic diseases and this increased risk is related to the pathophysiological changes seen in the cerebral vessels of patients with diabetes (18). Several studies demonstrated that the rate of IS in patients with diabetes mellitus was approximately 2 fold higher than in the non-diabetic, underlying that diabetes mellitus is a well-established independent risk factor for IS and is associated with high morbidity and total mortality in patients (8, 19-21). Additionally, some studies have indicated an association between diabetes mellitus and intracerebral hemorrhage (ICH), and diabetes was shown as an important risk factor for ICH (4, 22, 23). HbA1c is an established diagnostic index used to assess diabetes mellitus with a threshold of 6.5% for adults and also plays a critical role in the development of atherosclerosis in both diabetic and non-diabetic subjects (24, 25). The higher HbA1c level was positively correlated with future risks of stroke and coronary heart disease. In addition, HbA1c levels above 7.5% (58.5 mmol/mol) incrementally and significantly increased future risks of IS, coronary heart disease and early deterioration compared to HbA1c levels <5.5% (36.5 mmol/mol) (5, 26). In a study performed by Shafa et al., 150 diabetic and nondiabetic patients with acute ischemic stroke (AIS) were evaluated (27). They showed that the level of HbA1c can be used as a prognostic marker in nondiabetic patients with AIS. Li et al., also showed that elevated levels of HbA1c can be a useful serologic marker in evaluation of pathogenic condition and prognosis of IS in the brain stem lesions (28). In addition, they expressed that the HbA1c level is an independent risk factor in IS. In our study, results showed that the level of HbA1c in the IS group was significantly higher than that in the HS group. In a study by Sunaga et al., they concluded that the risk of stroke was related with the HbA1c level, especially in IS (29). In another study, Chmielewska et al., concluded that the HbA1c level was normal in the period of 2-3 weeks and 2-3 months prior to the occurrence of stroke in 21 patients with HS in the early stages of it (30). This finding is in line with our results.

Shuangxi et al. reported in a study that HbA1c levels were important predictors concerning the neurological disorder as well as the 3-month prognosis in patients with IS (31). The decline of HbA1c levels can reduce the severity of neurological deficits in these patients and improve the quality of life. Kamuchi et al., showed that HbA1c is a significant independent prognostic factor for functional and neurological outcomes using MRS and NIHSS criteria (32). Our results showed that there was a significant difference between the type with the extent of the lesion using imaging criteria, as well as the functional status of the patient using MRS criteria. The worse functional outcome and neurological disorder in patients with HS was inversely associated with a decrease in HbA1c level. In other words, increased levels of the HbA1c have a protective effect in preventing the deterioration of patient's functional status. These results were consistent with the study by Ibrahim et al., who showed that increased HbA1c level is associated with a better outcome in patients with intracerebral hemorrhage. They reported that there was an inverse relationship between HbA1c levels, volume of hematoma, ICH points, and MRS at discharge time (33). The study results of Mehta et al., also indicates a negative correlation between the volume of hemorrhage and HbA1c levels (34).

Wolf et al. reported that cigarette smoking is a significant independent to risk of stroke generally and brain infarction specifically (35). The results of this study showed that smoking is significantly related to a major lesion of ischemic stroke.

Conclusion

Our findings showed that there was a significant relationship between the HbA1c levels, the extent of the lesion and the functional status with the type of stroke (IS and HS). Our results also demonstrated that increasing HbA1c levels improves the function outcome of hemorrhagic patients using MRS score.

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