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ORGINAL ARTICLE

ROLE OF HBA1C ON SEVERITY AND FUNCTIONAL OUTCOME OF ISCHEMIC STROKE IN ELDERLY PATIENTS WITH DIABETES MELLITUS

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ABSTRACT

Introduction: Among all neurological diseases, stroke comes first in incidence and significance. Stroke is one of the common causes of death and disability all over the world.

Purpose of the study: To evaluate glycemic status effect represented by HbA1c on the stroke severity in patients with diabetes mellitus.

Patients and Methods: A prospective cohort study done in Neurology Department and Stroke – ICU of Internal Medicine, ZAGAZIG University Hospitals between Jan.2019 and Jul.2019. Study included 60 elderly patients with acute ischemic stroke divided into two main groups; acute ischemic stroke diabetics (Group I) (40 patients) and acute ischemic stroke non–diabetics (Group II) (20 patients). The diabetic group (Group I) was sub-grouped into poor glycemic control (Group Ia) with HbA1c >7 (20 patients), and good glycemic control (Group Ib) with HbA1c <7 (20 patients), and the non-diabetic group (Group II) with HbA1c < 5.7.

Results: There was a high statistically significant difference as regards fasting blood glucose and HbA1c between the studied groups (P-value < 0.001). We also found a statistically significant difference between the studied groups regarding stroke severity evaluated by NIHSS score and functional outcome after 3-months evaluated by mRS score with (p-value < 0.05).

Conclusion: Glycemic control has important relation on severity and outcome of ischemic stroke. HbA1c is an important predictor of acute ischemic stroke severity and prognosis in patients with diabetes mellitus.

Keywords: Acute ischemic stroke, Diabetes Mellitus, Glycated hemoglobin , Fasting blood glucose , functional outcome.`

INTRODUCTION

Among all neurological diseases, stroke comes first in incidence and significance, and its common presentation is an abrupt focal neurological deficit [1]. Ischemic stroke occurs due to sudden occlusion of a cerebral blood vessel [2]. About 20 million people every year suffer from stroke and 5 million of them will not stay alive [2]. About 85% of deaths from stroke occur in developing countries and stroke is a chief cause of neurological impairment, and 20% of those patients need care after 3 months, other complications of stroke, including seizures, brain edema pulmonary embolism, aspiration pneumonia, and fall [3].

Diabetes Mellitus is a risk factor for stroke, and the risk in diabetics is two times higher than in non-diabetics, furthermore their outcome is poorer than in non-diabetics [4]. Many studies revealed that residual neurological impairment and outcome are poor in diabetic patients when compared with non–diabetics [2]. Other risk factors as hypertension, dyslipidemia, obesity, reduced activity, smoking, and micro-albuminuria, all can share in the occurrence and worsen outcome of stroke in diabetic patients [3]. HbA1c reflects the mean control of blood glucose for the preceding 3 months [5]. American Diabetes Association recommends that a HbA1c level ≥ 6.5% is diagnostic for diabetes, compared with fasting blood glucose, HbA1c has a higher repeatability,

and can be done without fasting and is a steady marker for the glucose level [6].

Purpose of the study: To know the glycemic status by estimating the HbA1c, Fasting plasma glucose at admission among patients with acute ischemic stroke to study the effect of HbA1c on the severity of stroke at admission and functional outcome at the end of 3 months in acute ischemic stroke patients with diabetes and without diabetes and to compare the poor and good glycemic status patients among the diabetics for the competence of glycemic status on the severity and functional outcome of stroke.

PATIENTS AND METHODS

A prospective Cohort study was carried out on patients with acute ischemic stroke in Neurology Department and Stroke–ICU of Internal Medicine Department at ZAGAZIG University Hospitals between Jan.2019 and Jul.2019 (simple random). Sixty patient (60) had been selected and divided into two main groups; group I, acute ischemic stroke patients with diabetes (40 patient) and group II, acute ischemic stroke patients without diabetes (20 patient). Diabetics were sub-grouped into poor glycemic control (Group Ia) with HbA1c >7 (20 patient) and good glycemic control (Group Ib) with HbA1c <7 (20 patient).Control group (Group II) acute ischemic stroke patients without diabetes (20 patient) with HbA1c <5.7. Normal HbA1c level < 5.7 and ≥ 6.5 diagnostic for diabetes and measured by ELISA kits cobas C111. **Inclusion criteria:** Age ranging from 60 to 75 years old, both sex, males and females, diabetics and non-diabetics admitted with acute ischemic stroke.

Exclusion criteria: We excluded patients with intra cranial hemorrhage, those with central nervous system neoplasm, those with cerebral venous thrombosis, and those with recent cranial surgery or injury, and we excluded patients with suspected central nervous system infection, and those who might be lost during follow up for any reason other than death. **Ethical Clearance**: Written and informed consent was taken from some patients and from a first degree relative of patients with disturbed conscious level to participate in the study. Approval for performing the study was obtained from Internal Medicine Department, ZAGAZIG University Hospitals after taking Institutional Board Review (IRB) approval. This study has been carried out in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. All patients had been subjected to: thorough history taking, full clinical examination including general, heart, chest and abdominal examination and detailed neurological assessment using National Institute of Health Stroke Scale (NIHSS) to evaluate the severity of stroke at admission [7], and Modified Rankin Scale (mRS) to evaluate the functional outcome 3-months later after stroke onset [8]. All patients in this study were subjected to: Routine investigations in the form of: Fasting blood glucose, complete blood count, liver and kidney function tests, lipid profile, chest x-ray and ECG, special investigations in the form of: Glycated hemoglobin (HbA1c), plain brain CT and or MRI.

Statistical-analysis: All data were collected, tabulated and statistically analyzed using SPSS version 20.0 for windows (SPSS Inc., Chicago, IL, USA 2018). For categorical variables the values were represented as number and percentages. To test association between the groups, chi-square test had been used. For continuous variables, the values were represented as mean and standard deviation. To test the mean difference between three or more groups, ANOVA (Analysis of Variance) test with post hoc (Tukey's) test had been used. Multivariate logistic regression test also used. All tests were two sided. P-value < 0.05 was considered statistically significant (S), and p-value ≥ 0.05 was considered statistically non-significant (NS) and a p-value <0.001 is considered highly significant (HS).

RESULTS

There was no age or sex difference of statistical significance between the studied groups (p-value 0.596), also we noticed that stroke severity and functional outcome were not different between group Ib and group II (p-value 0.416) (table 1). Mean age of patients was 70.4±4.6 years. High mean LDL values noted in poor glycemic control patients, it had no statistically significant correlation. High mean HDL values were noted in good glycemic control patients and it had no statistical correlation between three groups (table 1).

In our study we found a high statistically significant difference between the studied groups as regard glycemic status (FBG and HbA1c) (p-value < 0.001), a high mean fasting blood glucose of 179.9 ± 9.1 mg/dl was noted in group Ia (Poor glycemic control) when compared to 122.7 ± 5.1 mg/dl in group Ib (good glycemic control) and 90 ± 8.41mg/dl in group II (non- diabetics), and group Ia had a high HbA1c level (8.9 ± 0.8) compared with group Ib (6.7±0.14) and group II (5.4 ±.04) (table 2).

We also noticed a statistically significant difference between the studied groups regarding stroke severity at admission evaluated by NIHSS score (p-value < 0.05), in group Ia 90.0 % of patients had moderate to severe stroke severity

(mean NIHSS 22.07±9.1) at admission, whereas 50.0% of patients in group Ib had mild severity (mean NIHSS 4±1.1), and 65% of patients in group II (non-diabetics) had mild stroke severity (mean NIHSS 3.6 ±1.1) (table 2, 3).

There was a statistically significant difference between the studied groups regarding stroke functional outcome after 3-months evaluated by mRS score (p-value< 0.05). A significant percentage of good glycemic control group (Group Ib) (75%) and the group without diabetes mellitus (Group II) (80%) of patients at 3 months follow up had functional independence (mean mRS 1.14±0.4), proportionally 55% of (Group Ia) at 3 months follow up had functional dependence (mean mRS 4.6±1.3) (table 2, 3).

Glycated hemoglobin had positive statistical correlation with stroke severity at admission and dependent functional outcome at 3-months of follow up between the studied groups (table 4).

Table 1: Demographic data and patients characteristics of the studied groups

		Group Ia (n=20)		Group Ib (n=20)		Group II (n=20)		X^2	P. value
		No.	%	No	%	No.	%		
Sex	**Male**	**11**	**55**	**7**	**35**	**9**	**45**		
	Female	**9**	**45**	**13**	**65**	**11**	**55**	1.035	0.596
Age (years)	**Range**	**65 -73**		**66-74**		**67-75**		**F.test**	0.563
	Mean±SD	**69.4±5.1**		**70.4±4.6**		**71.1±3.1**		.584	
T. cholesterol (TCL)	**Mean±SD**	**207.6 ± 47.6**		**199.78 ± 39.2**		**193.2 ± 48.6**		0.133	0.893
LDL	**Mean±SD**	**113. 8 ± 42.3**		**104.15 ± 31.4**		**102.8 ± 34.8**		0.954	0.388
HDL	**Mean±SD**	**45.3 ±14.6**		**46.0 ± 11.4**		**44.6 ± 13.3**		0.133	0.893
Triglycerides (TG)	**Mean±SD**	**181.5 ±76.8**		**171.12 ± 55.9**		**162.7 ± 44.0**		1.035	0.388
Hemoglobin	**Mean±SD**	**12.5±0.3**		**13.1±0.5**		**13.9±0.6**		0.965	0.382
Platelets	**Mean±SD**	**170±15.2**		**168±10.6**		**162±4.3**		0.132	0.829
WBCs	**Mean±SD**	**7.2±1.3**		**6.5±0.5**		**8.2±0.2**		0.133	0.385

TCL: total cholesterol; LDL: low density lipoproteins; HDL: high-density lipoproteins; TG: Triglycerides; WBCs: white blood cells

Table 2: Descriptive statistics for poor glycemic control (Gr Ia) and good glycemic control (Gr Ib) group and group II (Gr II)

		Group Ia (n=20)	Group Ib (n=20)	Group II (n=20)	chi-square	P. value
FBG mg/dl	**Mean ±SD**	**179.9±9.1**	**122.7 ±5.02**	**90±8.41**	**14.9**	0.001 (HS)
HbA1c%	**Mean ±SD**	**8.9±0. 8**	**6.7±0.14**	**5±0.4**	**7.3**	0.001 (HS)
NIHSS	**Mean ±SD**	**22.07±9.1**	**4 ±1.1**	**3.9±1.1**	**2.3**	0.01 (S)
mRS	Mean ±SD	4.6±1.3	1.14±0.4	1.13±0.4	2.7	0.01 (S)

FBG: fasting blood glucose; HbA1c: glycated hemoglobin; NIHSS: National Institutes of Health Stroke Scale; mRS: Modified Rankin Scale

Table 3 : Stroke severity at admission (NIHSS) and functional outcome at 3-months follow up (mRS) in the studied groups.

	Group Ia (n=20)		Group Ib (n=20)		Group II (n=20)		Total (100)%	chi-square	P
NIHSS	**N**	**%**	**N**	**%**	**N**	**%**			
***Mild (1-5)**	**2**	**10**	**10**	**50**	**13**	**65**	**41.6**		
***Moderate (6-20)**	**9**	**45**	**8**	**40**	**6**	**30**	**38.3**	**12.41**	**0.01 (S)**
***Severe (21-42)**	**9**	**45**	**2**	**10**	**1**	**5**	**20.1**		
mRS									
***Independent (0-2)**	**9**	**45**	**15**	**75**	**16**	**80**	**73**	**11.11**	**0.01 (S)**
Dependent* (3-6)	**11**	**55**	**5**	**25**	**4**	**20**	**27**		

NIHSS: National Institutes of Health Stroke Scale; mRS: Modified Rankin Scale

Table 4 : Multivariate logistic regression analysis model after adjusting the different parameters (age, sex, TCL, TG, LDL, Hb, WBCs, and platelets), only HbA1c was a risk factor for poor outcome.

Variables	Coefficients β	Std. Error	OR	*P*
HbA1c (%)	1.59	0.68	4.93	0.019(S)
Constant	-13.73			

DISCUSSION

High HbA1c level reflects poor glycemic control, and poor compliance to anti-diabetic treatment and it might have bad effects on the function of vascular tree including both micro and macro-vascular system leading to atherosclerosis [6]. Ischemic stroke is one of the clinical manifestations of cerebro-vascular disease and considered to be an end point of atherosclerosis [9]. Our main objective was to evaluate the relation between HbA1c and acute ischemic stroke severity at admission and its outcome at 3 months of follow-up in diabetic and non-diabetic patients.

Our study showed that there was a high statistically significant difference between the studied groups regarding their Glycemic status represented by fasting blood glucose (FBG) and glycated hemoglobin (HbA1c) (p- value < 0.001).Fasting blood glucose and glycated hemoglobin also had positive correlation between the studied groups of patients as regards severity of stroke at admission and poor outcome after 3 months. Poor glycemic control (group Ia) found to have high severity of stroke at admission and dependent outcome at follow up compared with both good glycemic control group (group Ib), and the non-diabetic group (group II). A high mean fasting blood glucose of 179.9 ± 9.1 mg/dl was noted in poor glycemic control group when compared to 122.7 ± 5.1 mg/dl in good glycemic control group and 90 ± 8.41 mg/ dl in the group without diabetes. Poor glycemic control had high HbA1c level (8.9 ± 0.8) compared with good glycemic control (6.7±0.14) and the group without diabetes (5±0.4), our results were matching with

Sunanda et al and **Hanan et al** who found a high significant difference as regards fasting blood glucose (FBG) and glycated hemoglobin (HbA1c) between the 3 studied groups; good glycemic control group, poor glycemic control group, and the group without diabetes (p-value < 0.001) [10,11].

In our study stroke severity at admission evaluated by National Institute of Health Stroke Scale (NIHSS) score and Stroke functional outcome at 3- months evaluated by Modified Rankin Scale (mRS) score, we found a statistically significant difference between the studied groups (p- value < 0.05), in poor glycemic control group (group Ia) 90.0% of patients had moderate to severe stroke severity (mean NIHSS 22.07±9.1) at admission. Whereas 50.0% of patients with good glycemic control (group Ib) had mild severity (mean NIHSS 4 ±1.1), and 65% of patients without diabetes had mild stroke severity (mean NIHSS 3.6 ±1.1), also there was a statistically significant difference between the studied groups regarding stroke functional outcome at 3- months of follow up (mRS) (p- value < 0.05). A significant percentage (75%) of good glycemic control group (group Ib), and (80%) of those without diabetes (group II) had functional independence (mean mRS 1.14±0.4), and 55% of Group Ia had functional dependence (mean mRS 4.6±1.3) at 3 months of follow up, this was in agreement with **Sunanda et al** who revealed that there was high statistically significant difference (P- value < 0.001) as regard NIHSS score and mRS score in the three groups of patients. Patients with high HbA1c and high fasting blood glucose, their NIHSS score was high and their outcome was poor (P- value < 0.001), also **Baghel et al** found a high statistically significant difference as regards stroke severity at admission evaluated by NIHSS score between the diabetics in one arm and pre and non-diabetics on the other arm (p-value <0.001), he found also a high statistically significant difference as regards stroke functional outcome evaluated by mRS score between non-diabetics in one arm and pre and diabetics on the other arm (p-value < 0.001) [10,12].

Hanan et al also found a high statistically significant difference as regards stroke severity at admission evaluated by NIHSS score between the poorly controlled diabetics in one arm and good controlled diabetics and non–diabetics on the other arm (p-value< 0.001) [11].

Our results also were in agreement with **Kuwashiro et al** who studied 3627 patients with acute ischemic stroke, and found that neurological enhancement is poorer relevant to the high levels of glycated hemoglobin (HbA1c), also suggests that HbA1c levels may influence the severity of ischemic stroke and predict its prognosis. [13]. So, HbA1c could be a chief predictor for neurological impairment and prognosis in patients with acute ischemic stroke, therefore lowering HbA1c level may reduce the severity of neurological impairment of ischemic stroke and improve its functional outcome at 3 months follow up.

Limitations of our study were that the infarct size was not measured by CT or MRI, however NIHSS score is a good clinical measure of stroke severity, which parallels the infarct size, other diabetic complications and other underlying risk factors for ischemic stroke as dyslipidemia, smoking, and hypertension weren't considered during the follow up period which might affect the prognosis.

CONCLUSION

In patients with diabetes mellitus the severity of deranged glycemic status represented by HbA1c found to have a major effect on the stroke severity and functional outcome. Glycemic control has important relation on severity and outcome of ischemic stroke. HbA1c is an important predictor of acute ischemic stroke severity and prognosis in patients with diabetes mellitus.

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