Cerebrovascular Accidents in Diabetic Patients: Can HBA1c Predict Early Outcome and Mortality?

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ABSTRACT

Background: Stroke is the second largest cause of death in adults and more than 20% of diabetic patients are affected. Hyperglycaemia during the period a person suffers from stroke is reported to be associated with poor outcome and survival.

Objective: To analyse the predictive power of glycated haemoglobin (HBA1C) for early functional outcome in terms of modified Rankin Score and early overall survival.

Methods: Prospective observational study conducted at the department of Internal Medicine between July 2015 and December 2016. Diabetic patients who presented with stroke between 45 and 70 years of age were included. All patients were investigated with random blood glucose levels and HBA1C at the time of admission. A receiver operating characteristic (ROC) curve analysis was performed to determine the predictive power of HBA1C on early outcome in terms of modified Rankin Score at discharge and early overall survival.

Results: Of the 146 patients included in this study, there were 48 (32.9%) males and 98 967.1%) females with a mean age of 56.88 ± 4.67 years (range: 47-69).69 (47.3%) cases had their random blood sugar (RBS) of more than 200 mg/dL. The mean HBA1C at the time of admission was 8.17 ± 1.64 %.The mortality rate was 21.2% (n = 31) and mean mRS at the time of discharge was 3.75 ± 1.56.A ROC curve was obtained utilising the HBA1C levels against the outcome categorised as favourable (mRS ≤3 at discharge) or unfavourable (mRS ≥3 at discharge). The ROC curve was significant (p <0.0001) with an area under the curve (AUC) of 95% (95% confidence interval (CI) 0.92 to 0.99). At the cut-off limit of 7.5% of HBA1C, the sensitivity was 91.9% and specificity of 91.7%.

Conclusion: The glycated haemoglobin level is a strong predictor of functional outcome as well as in-hospital mortality. It may be used as a prognostic tool to direct intensive therapies in diabetic stroke patients.

Keywords: Cerebrovascular accident, stroke, diabetes, Hemoglobin A1C, HBA1C

Introduction

Cerebrovascular accidents (CVAs) are the largest cause of disability and second leading cause of mortality in 45 to 80 years age groups. CVAs are particularly common in diabetic patients and epidemiological studies have estimated that more than 20% patients with CVAs are diabetics.[1, 2]Similarly, diabetes increases the relative risk of stroke by 2.3 times and it corresponds with the high tertile of HBA1C or the glycosylated haemoglobin percentage. Hyperglycaemia at the time and soon after stroke is a poor predictor of outcome.[3, 4]

Several studies[5, 6] have reported conflicting outcome data regarding stroke in diabetes, hyperglycaemia and glycaemic control, with some large studies even showing that patients without diabetes with hyperglycaemia at the time of stroke have worse outcome as compared to those with diabetes.[5, 6] This rise in blood glucose is termed as stress hyperglycaemia.[7] A look into the data of these patients points toward presence of subclinical DM or prediabetes around the time of stroke, whereby they were included in the non-diabetic population and hence had an effect on the outcome data.[8]

The Heart Disease and Stroke update 2016 edition from the American Heart Association (AHA) and Centre for Disease Control (CDC) has revealed that prediabetes is highly common among stroke patients and its prevalence is around 38% of the current population.[9]

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Li et al, on the other hand investigated the role of HBA1C on the severity and outcome of stroke patients, without taking into account the pre-stroke diagnosis of DM.[10] They showed that higher HBA1C levels relate directly to the severity of the CVAs with poor outcome.[10] However, the confirmatory data is insufficient. Recently, the American Diabetes Association (ADA) recommendations included the use of HBA1C for the diagnosis of prediabetes, hence to direct efforts for effective management.[11, 12] Prediabetes is identified to affect the early and long-term outcome; however, the data regarding the effectiveness of the predictive power of HBA1C is still scant.[13]

Our aim in this study was therefore, to analyse the effect of HBA1C levels in CVAs on early outcome (<30 days) in terms of modified Rankin score (mRS) and mortality. We asked the question, as to how much predictive power the HBA1C had in terms of early stroke outcome. Establishing HBA1C as the predictor of stroke outcome, it may provide a strong evidence base for prognostication of stroke patients and better management.

Methods

This is a prospective observational study conducted at the department of Internal Medicine between July 2015 and December 2016 (18 months) after obtaining permission of the institutes' ethical committee. At inclusion in the study, an informed consent was obtained from the patients or their relatives.

We included diabetic patients between the ages of 45 and 70 years from both genders irrespective of their stroke or diabetes subtype. Patients with traumatic ischaemic or haemorrhagic infarctions, those with aneurysmal, cardiovascular origin embolic or any interventional procedure related infarctions or intracerebral haemorrhages (ICH) were, excluded. Confirmation of stroke using a non-enhanced CT scan of the brain on emergency basis was done once the patient was stabilised medically.

We collected data on a digital chart about patient age, gender, vitals, stroke type, diabetes subtype and duration, treatment type of diabetes, comorbidities, body mass index (BMI), admission lipid profile, hyperglycaemia and HBA1C. All patients were categorised using the modified Rankin Scale (mRS) at the time of admission and discharge.

All patients were provided the best medical management in a high dependency stroke care unit with multidisciplinary board overlooking the entire management.

The data was uploaded to SPSS version 22.0 and analysed using appropriate statistical tests. All continuous variables were presented using mean ± standard deviation while categorical variables were presented using frequencies and percentages. A Receiver Operating Characteristic Curve analysis was done for the predictive power of HBA1C regarding outcome of these patients in terms of mRS at discharge. Similarly, a binary logistic regression was performed for assessing the role of various clinical risk factors regarding in-hospital mortality. A level of ≤0.05 was established as indicator of statistical significance.

Results

Of the 146 patients included in this study, there were 48 (32.9%) males and 98 967.1%) females with a mean age of 56.88 ± 4.67 years (range: 47-69). Among the study population there were 120 (82.2%) patients between the 45 and 60 years while the rest 26 (17.8%) were between 60 and 70 years age group. The mean mRS at admission was 3.9 ± 1.02. There were 125 (85.6%) cases of ischaemic stroke and 21 (14.4%) cases of haemorrhagic stroke. 15 (10.3%) cases were of type 1 diabetes while the rest 131 (89.7%) were type 2 diabetes patients. Majority (n = 73, 50%) of these diabetic patients were on oral hypoglycaemic drugs. The mean diabetes duration at the time of presentation was 11.08 ± 6.49 years.

The mean systolic blood pressure at the time of admission was 149.6 ± 27.79 mm Hg while there were 51 (34.9%) cases of pre-stroke hypertension and 15 (10.3%) cases of pre-stroke ischaemic heart disease (IHD). 16 (11.0%) patients had a history of previous stroke while 32 (21.9%) were current smokers.

69 (47.3%) cases had their random blood sugar (RBS) of more than 200 mg/dL. The mean HBA1C at the time of admission was 8.17 ± 1.64 %. Mean serum triglycerides (TGDs) were 116.5 ± 7.8 mg/dL and the mean cholesterol was 151.6 ± 12.4 mg/dL. Mean BMI was 25.27 ± 3.03 while the average length of stay (LOS) was 9.89 ± 3.7 days. The clinical and laboratory parameters are classified according to the two outcome groups (**Table 1**)

The mortality rate was 21.2% (n = 31) and mean mRS at the time of discharge was 3.75 ± 1.56. At the time of discharge, 74 (50.7%) patients were having a mRS of ≤3 (favourable outcome) while 72 (49.3%) patients had a mRS of ≥3 (unfavourable outcome).**Table 1**

Table 1: Clinical and laboratory parameters for the two outcome groups

Clinical variable	Favourable outcome (mRS ≤3)	Unfavourable Outcome (mRS ≥3)	P value
Age	55.6 ± 4.1 years	58.2 ± 4.8 years	**0.001**
mRS admission	3.6 ± 1.05	4.2 ± 0.9	**0.001**
DM duration	10.9 ± 6.4 years	11.24 ± 6.6 years	0.77
Systolic BP	143.2 ± 19.8mmHg	156.2 ± 32.9mmHg	**0.004**
HBA1C	6.89 ± 0.45%	9.5 ± 1.4%	**<0.0001**
Triglycerides	117.08 ± 8.04mg/dL	116.03±7.7mg/dL	0.42
Cholesterol	151.8 ± 13.2mg/dL	151.5±11.6mg/dL	0.85
BMI	25.4 ± 3.1	25.1 ± 2.9	0.59
LOS	9.1 ± 3.5 days	10.6 ± 3.9 days	**0.02**

BMI: Body Mass Index, DM: Diabetes Mellitus, HBA1c: Hemoglobin A1C, LOS: Length of Stay mRS: Modified Rankin Scale

A ROC curve was obtained utilising the HBA1C levels against the outcome categorised as favourable (mRS ≤3 at discharge) or unfavourable (mRS ≥3 at discharge). The ROC curve was significant (p <0.0001) with an area under the curve (AUC) of 95% (95% confidence interval (CI) 0.92 to 0.99). At the cut-off limit of 7.5% of HBA1C, the sensitivity was 91.9% and specificity of 91.7%. Similarly, at the cut-off limit of 7.0%, the sensitivity and specificity were 68.9% and 95.8%, respectively.
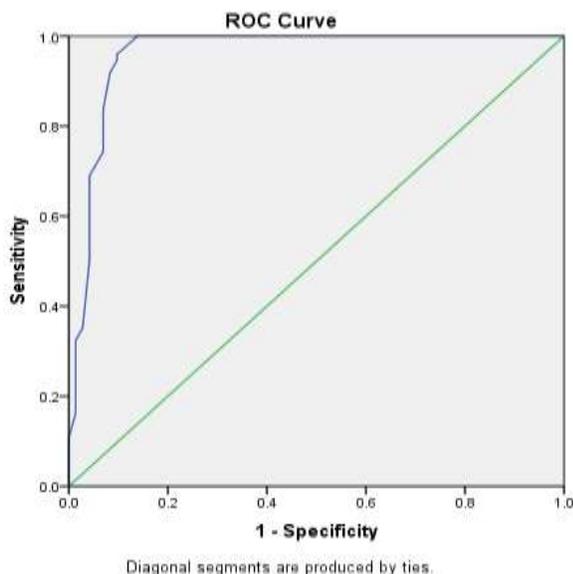

Figure 1: Receiver operating characteristic curve analysis for HBA1c as predictor of functional outcome in terms of modified Rankin Score

A logistic regression was performed to ascertain the effects of age, gender, BMI, systolic BP, past history of stroke, current smoking history, RBS of >200 mg/dL at admission, HBA1C and lipid profile on the likelihood of in-hospital mortality. The logistic regression model was statistically significant, $\chi^2(21) = 109.55$, p < 0.0001. The model explained 81.9% (Nagelkerke R^2) of the variance in mortality and correctly classified 91.8% of cases. Of the twelve predictor variables, three were statistically significant: past history of stroke, smoker and HBA1C (as shown in). For every 1.09% reduction in HBA1C, the likelihood of in-hospital mortality reduced by 3.3 times (95% CI: 1.8 to 6.1, p <0.0001). The regression model predicted a sensitivity of 71% and specificity of 95.7% for predicting in-hospital mortality for the risk factors cited above.(**Error! Reference source not found.**)

Table 2: Logistic regression analysis for the twelve clinical, laboratory variables, and their effect on in-hospital mortality

	B	df	P value	Odds Ratio	95% C.I. for OR	
					Lower	Upper
Age	-0.09	1	0.37	0.92	0.76	1.11
Gender (male)	1.77	1	0.090	5.86	0.76	45.12
mRS @ admission	-0.27	1	0.53	0.76	0.33	1.78
DM duration	-0.05	1	0.46	0.95	0.84	1.08
Systolic BP	0.003	1	0.80	1.003	0.98	1.03
Previous Stroke	-6.78	1	**0.003**	0.001	0.00	.09
Smoker	-2.13	1	**0.035**	0.12	0.02	.86
RBS > 200 mg/dL	-0.32	1	0.65	0.72	0.17	2.97
HBA1C	-1.09	1	**<0.0001**	0.34	0.18	.61
Triglycerides	0.05	1	0.31	1.06	0.95	1.18
Cholesterol	0.06	1	0.15	1.06	0.99	1.15
BMI	-0.06	1	0.62	0.94	0.73	1.21
Constant	4.42	1	0.68	83.36	--	--

BMI: Body Mass Index, DM: Diabetes Mellitus, HBA1c: Hemoglobin A1C, mRS: Modified Rankin Scale, RBS: Random Blood Sugar

Discussion

Our study has investigated the close association between increasing levels of glycated haemoglobin levels and early outcome in terms of mRS and mortality. A few conclusions can be made from the results, that are supported by several large and well-designed studies: hyperglycaemia not only at the time of stroke, but at several weeks before stroke is

predictive of stroke severity[5, 12, 14]; hyperglycaemia in the form of glycated haemoglobin levels can predict poor or favourable outcome with high sensitivity and specificity in terms of mRS at discharge and in-hospital mortality.[10, 15]The demographic and clinical characteristics of our study are in agreement with many other studies.[9, 13, 16, 17] Stroke is most common during the 45 to 60 year age group of diabetic patients while in non-diabetics, slightly older population is affected. Women with diabetes are more commonly affected as compared to males.[17, 18]This demographic trend is contrary to the gender differences in patients without diabetes. More than one third of diabetic patients with stroke have pre-stroke hypertension, while around 10% have concomitant ischaemic heart disease.[9]

In the past, several studies have shown the close correlation between hyperglycaemia and unfavourable stroke outcome or early mortality.[1, 6, 19]Others have shown that hyperglycaemia irrespective of pre-stroke diagnosis of diabetes still affect outcome.[8, 20]Some contradict these reports, where they have shown that hyperglycaemia in patients without diabetes is more detrimental than merely a diagnosis of diabetes that is in good control.

Hjalmarsson and associates have shown that hyperglycaemia correlates to higher mortality; however, prestrike controlled hyperglycaemia is not predictive of poor outcome.[21] They have shown that hyperglycaemia may not be associated with the severity of stroke in an independent manner and it may not be associated with poor outcome at one year after stroke.[21]On the contrary, they have shown that good glycaemic control prior to stroke is the determinant of good neurological recovery and higher survival. This was shown by the correlation of HBA1C and severity of the stroke irrespective of the pre-stroke diagnosis of diabetes.[21, 22]It is also important to note that HBA1C is correlated with poor outcome in an incremental way in our study as well.(**Error! Reference source not found.**)

Studies from the Fukuoka stroke registry has shown that high levels of HBA1C are independent predictors of poor outcome after stroke.[14, 17, 23]We have shown these effects in our ROC curve analysis, with an AUC of 95% (95% CI, 92 to 99). Though we did not investigate the subtype of stroke in our patient population, several large studies have shown that no correlation exist between HBA1C levels and CVA lesion according to TOAST criteria.[24] Our multivariate analysis also shows significance for prior history of stroke and smoking as the independent predictors of in-hospital mortality. Poor glycaemic control as manifested by higher HBA1C levels, smoking and past history of stroke have important pathophysiological impact on the overall structural and functional effects on brain vasculature, thereby leading to earlier and severe stroke.[15, 25]This is in agreement with the findings of Vermeer and co-workers[26] who concluded that a prior history of transient ischaemic attack (TIA) or stroke nearly doubles the risk of death after subsequent attacks. The severity of stroke and the negative physiological effects of hyperglycaemia eventually translates into poor overall functional outcome after stroke and high mortality.[26]

Our study did not show any significant mean difference for the type and duration of diabetes to affect early functional recovery or mortality. There was also no association observed between the type of stroke, mean systolic BP at the time of admission and the effect of cholesterol or triglycerides levels on early outcome, although research points towards untoward impact of these risk factors in long-term outcome after stroke.[27]

This was a single centered study which included patients of the same population being exposed the same risk factors and environment. Certain other confounding factors such as environmental factors, diet, job opportunities, lifestyle, and socioeconomic status were not taken into account which can directly and indirectly impact the incidence of cerebro-vascular events in diabetic patients. Since the relationship of these confounding factors tends to be different for different countries and regions, further prospective and meta-analytic studies including studies under different settings will help in assessing the significance of these factors leading to cerebro-vascualr events in diabetic patients.

Conclusion

Cerebrovascular accidents affect younger age patients with diabetes, females more than male patients. Hyperglycaemia, even if present for several weeks before the episode of a cerebrovascular accident is predictive of early functional neurological outcome and mortality in the form of glycated haemoglobin. Previous history of stroke and current smokers are at increased risk of death in this population.

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