"A STUDY TO ANALYSE THE ROLE OF HbA1C IN THE RISK PREDICTION OF ISCHEMIC STROKE AND TRANSIENT ISCHEMIC ATTACKS"

ABSTRACT:

BACKGROUND:

Stroke is the second most important cause of mortality worldwide. Diabetes mellitus is a major risk factor for the development of stroke, particularly ischemic stroke. Epidemiological data show an increased risk of stroke associated with hyperglycemia. For example, in the Framingham Study the incidence of thrombotic stroke was 2.5 times higher in diabetic men and 3.6 times higher in diabetic women than in those without diabetes. However, the prevalence of hyperglycemia preceding cerebrovascular events is poorly defined, so the relative importance of hyperglycemia as a risk factor is uncertain. In particular, the importance of mild hyperglycemia, as opposed to symptomatic diabetes, as a precursor of stroke is unclear. Measurement of glycosylated hemoglobin (HbA1c), in patients with recent stroke or transient ischemic attacks (TIA) has allowed us to address this question.

AIMS AND OBJECTIVES:

1. *To estimate the correlation between glycosylated hemoglobin levels and ischemic stroke/transient ischemic attacks.*
2. *To investigate the usefulness of glycosylated hemoglobin in accurately assessing the glycemic control in stroke and transient ischemic attack patients as compared to capillary glucose levels.*

METHODS:

This hospital based study was performed in King George hospital,Visakhapatnam,AndhraPradesh from May 2019 to August 2020.A total of 200 patients admitted with ischemic stroke and transient ischemic attacks were included in the study.All the subjects were interviewed,examined and investigated as per the predesigned proforma.

RESULTS:

Out of 200 patients studied 23 had TIA and 177 had ischemic stroke. 43.47% of TIA patients had HbA1c ≥6.5%. 68.92% of ischemic stroke patients had HbA1c≥6.5%. 52.11% patients who had RBS<200mg/dl had HbA1c≥6.5%. 58.69% patients of known diabetic history had HbA1c≥6.5%. 68.18% patients with no known diabetic history had HbA1c≥6.5%.

CONCLUSION:

Hyperglycemia recognized or unrecognized is a major risk factor for stroke. HbA1C may be a better indicator of glycemic status than RBS in stroke.Achieving an HbA1c target of less than 7% in diabetic patients is very important to prevent stroke.

Keywords:*Transient ischemic attack(TIA);Random blood sugar(RBS);Glycosylayed hemoglobin (HbA1c)*

1.INTRODUCTION:

Stroke remains the second-leading cause of death and the third-leading cause of death and disability combined in the world. The rapid socioeconomic changes in INDIA during recent years have led to changes in lifestyle and diet that can influence the risk factors for diseases such as stroke.[(1)] Diabetes mellitus is a major risk factor for the development of stroke, particularly ischemic stroke, with the type 2 diabetes mellitus alone known to increase risk by 1.5 to 4 fold.[(2)] Macrovascular complications

of diabetes mellitus (ischemic heart disease, stroke, peripheral vascular disease) represent a major cause of diabetes mellitus related mortality and health care expenditure. [3] Chronic elevation of blood glucose levels leads to damage of blood vessels. The endothelial cells lining the blood vessels take in more glucose than normal, since they do not depend on insulin. Then they form more surface glycoproteins than normal, and cause the basement membrane to grow thicker and weaker. In diabetes, the resulting problems are grouped under “microvascular disease” (due to damage of small blood vessels) and “macrovascular disease” (due to damage of arteries). Epidemiological data show an increased risk of stroke associated with hyperglycemia. [4] For example, in the Framingham Study the incidence of thrombotic stroke was 2.5 times higher in diabetic men and 3.6 times higher in diabetic women than in those without diabetes. However, the prevalence of hyperglycemia preceding cerebrovascular events is poorly defined, so the relative importance of hyperglycemia as a risk factor is uncertain. In particular, the importance of mild hyperglycemia, as opposed to symptomatic diabetes, as a precursor of stroke is unclear. Measurement of glycosylated hemoglobin (HbA1c), which reflects glycemic levels for the preceding 1-3 months , in patients with recent stroke or transient ischemic attacks (TIA) has allowed us to address this question.

2.MATERIALS AND METHODS

STUDY SETTING: All the patients who have been admitted with ischemic stroke and transient ischemic attacks in the General Medicine ward in King George Hospital, Visakhapatnam from May 2019 to August 2020 were included in the study.

SAMPLE SIZE: Total number of patients in this study will be 200.

INCLUSION CRITERIA:

All male and female patients admitted with ischemic stroke and transient ischemic attacks irrespective of their previous glycemic status,smoking history,hypertension,cholesterol levels and past history of stroke.

EXCLUSION CRITERIA:

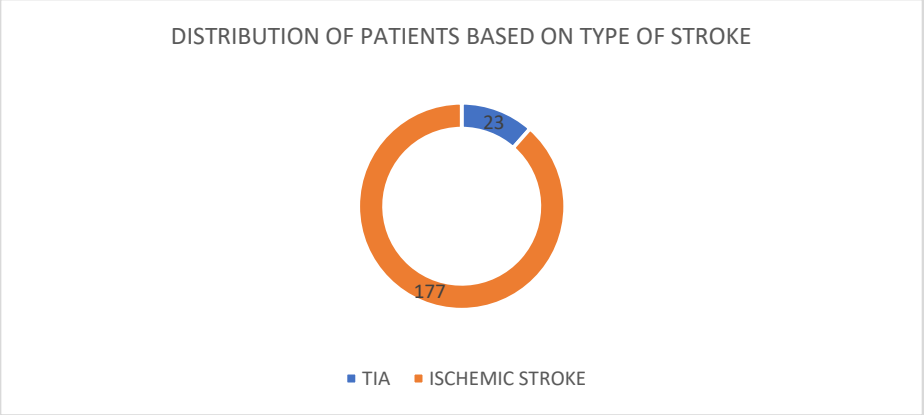
Hemorrhagic stroke,cardioembolic stroke,stroke mimickers-unusual manifestations of nonvascular conditions that may resemble acute stroke syndrome,intracranial tumors,hypertensive encephalopathy,multiple sclerosis,psychiatric problems,factitious disorders.

After through history taking and detailed neurological examination confirmation of diagnosis was done by CT or MRI brain. HbA1C levels and RBS at the time of admission were noted and evaluated.

RESULTS:

Graph 1: Distribution of patients based on type of stroke

Out of 200 patients studied 23 were found to have TIA and 177 were found to have ischemic stroke.



Graph 2: Distribution of patients based on RBS(mg/dl)

Out of 200 patients studied mean RBS was 205.96mg/dl.

Range – 55 to 512 mg/dl

Out of 200 patients 142 had RBS less than or equal to 200 mg/dl

58 had RBS more than 200 mg/dl

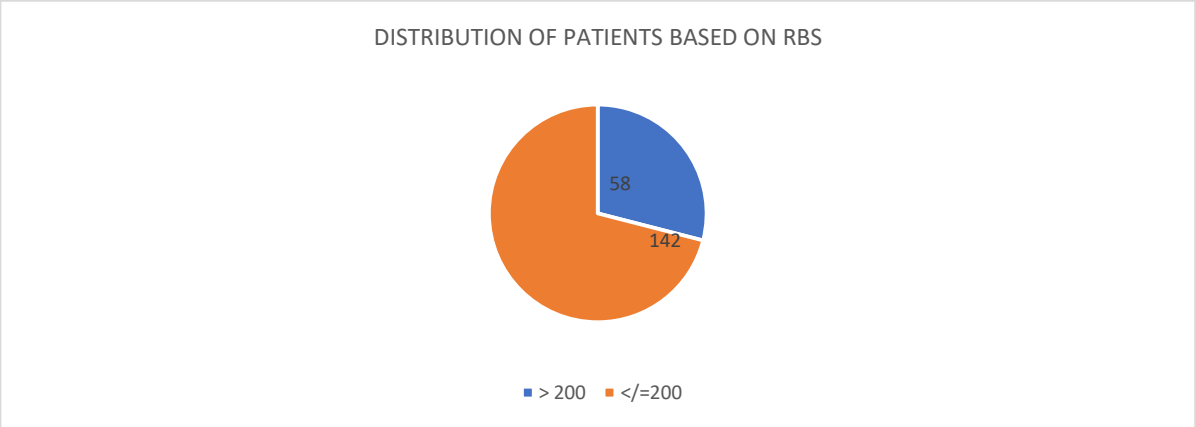


Table-1 : Distribution of patients based on HbA1c levels(%)

Table Showing Distribution of Stroke patients based on HbA1c						
			HbA1c			Total
			4-6%	6.1-6.4%	≥6.5%	
	Ischemic	Number	13	42	122	177

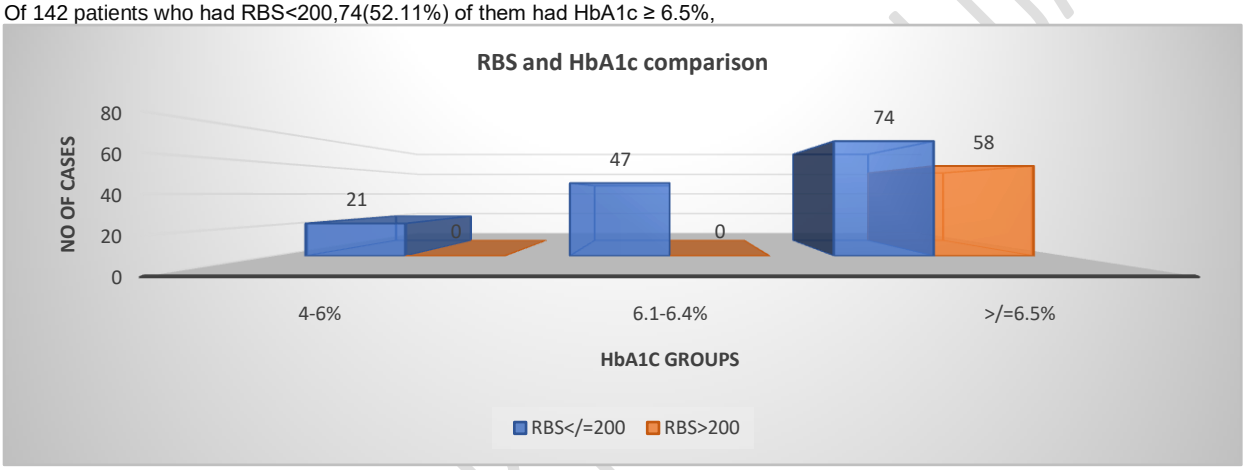
Stroke	Stroke	Percentage	7.34%	23.72%	68.92%	100%
	TIA	Number	8	5	10	23
		Percentage	34.78%	21.73%	43.47%	100%
Total		Number	21	47	132	200
		Percentage	10.5%	23.5%	66%	100%

Out of 23 TIA patients 10(43.47%) had HbA1c of ≥6.5%

Out of 177 patients with ischemic stroke 122(68.92%) had HbA1c of ≥6.5.

Graph 3: RBS and HbA1C comparision

Of 142 patients who had RBS<200,74(52.11%) of them had HbA1c ≥ 6.5%,



All 58 who has RBS>200, had HbA1c ≥ 6.5%

Table 2:

RBS and HbA1c comparison						
			HbA1c			Total
			4 – 6%	6-6.4%	≥6.5%	
RBS	Less than 200	Number	21	47	74	142
		Percentage	14.78%	33.0%	52.11%	100%
	More than 200	Number	0	0	58	58
		Percentage	0.00%	0.00%	100%	100%
Total		Number	21	47	132	200
		Percentage	10.5%	23.5%	66%	100%

P VALUE IS <0.00001. SIGNIFICANT AT P<.05

Mean HbA1c in patients with RBS <200 was 6.76%.

Mean HbA1c in patients with RBS >200 was 8.11%.

Table 3: HbA1c and RBS among patients with known diabetics

Diabetic status known N=46	Mean HbA1c(%)	Mean RBS(mg/dl)	Mean age(yrs)
	7.06	204.93	60.13

27 out of 46 patients(58.69%) had HbA1c of ≥ 6.5%, and among these people 20 of them(74%) had HbA1c of > 7%,signifying that is their glycemic target was not achieved.

14 out of 46 patients(30.43%%) had RBS >200.

Table 4: HbA1c and RBS among patients with diabetic status unknown

Diabetic status unknown N=154	Mean HbA1c(%)	Mean RBS(mg/dl)	Mean age(yrs)
	7.18	206.27	60.38

105 out of 154 patients (68.18%) had HbA1c of ≥ 6.5%

44 out of 154 (28.57%) patients had RBS>200mg/dl.

110 out of 154 (71.42%) patients had RBS</=200mg/dl.

DISCUSSION

Stroke is the sudden onset of a neurological deficit caused by an acute focal injury to the central nervous system due to a vascular cause. It is a common disorder with dire consequences for the patient and society. The incidence of strokes occurring every year worldwide is about 17 million.Following the stroke, many patients, unfortunately, suffer a further stroke, and recurrent strokes account for approximately 25% of the total. Considerable scope, therefore, exists to improve both primary and secondary stroke prevention. The prevalence of stroke is affected by various modifiable risk factors, including the degree of glycemic and blood pressure control, smoking, presence of hyperlipidemia and nonmodifiable risk factors, including age, male gender, duration of diabetes. Diabetes is an independent risk factor for athero-thrombotic brain infarction at all ages. Epidemiological data show an increased risk of stroke associated with hyperglycemia.[5]

People with diabetes have chronic impairment of cerebral blood flow and autoregulation, lower white and red blood cell deformability, hyperviscosity, endothelial dysfunction, hypercoagulability, impaired prostacyclin synthesis that increase platelet adhesiveness, and possible dysfunction of cortical arteriolar smooth muscle and endothelium, which are essential for collateral flow. In diabetic patients, several mechanisms suggest that prolonged hyperglycemia leads to stroke. These include vascular endothelial dysfunction, increased early-age arterial stiffness, systemic inflammation, and thickening of the capillary basal membrane.[6] Hyperglycemia may predispose to infarction when present at the time of ischemia and to poor recovery from stroke. It commonly precedes stroke in those with previously undiagnosed diabetes. Pulcinella et al. reported that both diabetics and nondiabetics who were hyperglycemic at the time of stroke, as measured by admission blood glucose, did worse.

Evidence suggesting a significantly increased prevalence of glucose intolerance among persons with cerebrovascular disease has long been available. Jakobsen studied patients with cerebrovascular disease without overt diabetes, finding 21% with abnormal glucose tolerance (Fajans & Conn Criteria) and 50% with abnormal Predinsone – augmented glucose tolerance tests. Gerter and his colleagues in a population with thrombotic stroke found overt diabetes in 30% and Abnormal glucose tolerance (Fajans & Conn criteria) in 59% of rest. They concluded that over 70% of their stroke population had overt or covert diabetes mellitus. However, these striking figures have attracted little attention. This is because of an entity called"stress hyperglycemia," which could be a cause of raised glucose levels in acute stroke patients. Causes of stress hyperglycaemia are:

1.the stress response to an acute vascular event

2.ensuing physical inactivity and inadequate food intake

3.use of IV fluids before the event / during the event

Thus glucose intolerance in stroke patients may or may not reflect glycemia before the event—the measurement of HbA1c rather than glucose as an indicator of prior glycemia addresses this problem. Since the erythrocytes survive about three months, HbA1c measurements in patients with normal erythrocyte survival reflect plasma glucose concentration during that period. Even if the cerebrovascular event resulted in marked and sustained plasma glucose elevation in a previously normoglycemic person, it would have a little effect on HbA1c measured. Another attractive feature of the HbA1c assay is that it presumably reflects the generalized tissue effect of hyperglycemia.

HbA1c has a direct relationship with mean glycemia because erythrocytes are continuously glycated during their 120–day lifespan. In the diabetes control and complication trial, a HbA1c level of 6% corresponded to a mean serum glucose level of 135 mg/dl. HbA1c test can be used to diagnose pre-diabetes or diabetes and check the long-term control of blood glucose levels in people with diabetes. Serum blood glucose level changes during the day for many reasons, including medicine, diet, exercise. While the HbA1c test result is not affected by any recent changes. An increased HbA1c level reflects poor long-term glycemic control and has its specific implications on vascular beds' structure and function, including small as well as large cerebral vessels.

Transient Ischemic Attack is a known predictor of subsequent ischemic stroke with risk estimates within three months between 7.5% and 17.3%; half of those events were described to occur within 48 hours.TIA carries an exceptionally high short-term risk of stroke, and TIAs precede approximately 15% of diagnosed strokes. 7% to 40% of the stroke patients are found to have a history suggestive of TIA episodes.[7]The incidence of transient ischemic attack (TIA) is somewhat more complicated to establish, as many TIAs may go unreported, particularly in older populations with multiple medical disorders. The ABCD2 score was developed to predict individual risk and to triage patients on the first presentation.

Of the 200 patients studied, 23(11.5%) were found to have TIA, and 177 were found to have an ischemic stroke. In a study by IYAD ALI et al., 11% of patients had transient ischemic attacks.

In our study, out of 200 patients, 142 (71%)had RBS less than or equal to 200 mg/dl, 58(29%) had RBS more than 200 mg/dl. In a study by D.M Bravata et al ., 95% has RBS less than 200mg/dl, and 5% had RBS more than 200mg/dl.[8] In a study by Niaz Ahmed et al., RBS is greater than 200 in 6.9% of patients.[9] In a study by DR D.R Gunasekharan et al., 56% of patients had hyperglycemia at the time of admission (RBS >/=200mg/dl).

The mean HbA1C in our study is 7.153±1.17%, which is lower when compared to the mean HbA1C of 8.89% in a survey by Khalid Al-Rubeaan et al., and a mean HbA1C of 7.7±1.9%, in a study by VERANNA MOHAN GADAD et al.,The mean HbA1C in our study is higher than the mean HbA1C in a survey by Sumaira Nabi et al., which is 5.9±2.9%.

In a study by john Peter Mitsios et al., diabetes mellitus range HbA1c (≥6.5%) was associated with a significantly increased risk of first-ever stroke compared to non– diabetes mellitus range HbA1c.In our study of 200 stroke patients, 132 (66%) had HbA1c ≥ 6.5%, which indicates that they had impaired glucose tolerance even before the insult occurred. But in a study by Asgard A Abdalgbar et al., only 25% of patients with acute ischemic stroke had an HbA1C value≥ 6.5%. In a study by wai Kwong tang et al., 13.2% had HbA1c >6.5% (min 3.1%, max 14.9%) on admission to hospital, while in a study by IYAD ALI et al., 51.4% had HbA1c levels equal or greater than 6.5%. In a study by Dr. Prachi Pratichi Das et al., HbA1c is ≥ 6.5% in 64.57% of patients admitted with stroke supporting our study.

Most current guidelines circulated by professional associations for diabetes, including the American Diabetes Association, recommend HbA1c <7% as the optimal target for glycemic control.[10] Poor glycemic control would eventually contribute to a high risk of diabetic comorbidities such as stroke in patients with type 2 diabetes. However, studies with regard to this topic have shown inconsistent results.[11] In the early 1990s, results from the United Kingdom Prospective Diabetes Study (UKPDS) showed that patients with HbA1c level less than 6.3% did not have a significantly lower risk of first-ever stroke than patients with HbA1c level between 6.3% and 7.6% and even those with HbA1c level >7.6%. Another group using a large public health database also showed a non-significant association between HbA1c and stroke risk.[11] Kizer JR et al., studied the relationship between HbA1c and stroke.[12] The results showed that HbA1c and stroke risk was significantly associated. The mechanism might be that long term high blood glucose and high blood HbA1c may lead to lesions of large blood vessels, nerve tissue ischemia, and hypoxia, that is not of benefit for the recovery of neurological function, and the prognosis is worse. They emphasized that strict control of glycated hemoglobin (HbA1c) might be a benefit for stroke prevention for patients with diabetes. A recent study by Li et al., was one of the few studies systematically investigating the role of HbA1c on stroke outcome, regardless of a prestroke diagnosis of DM; their results showed that elevated HbA1c level is related to stroke severity and poor prognosis in the whole study population; however, only patients with brainstem infarction were included in this study.[13]

Although many studies have reported a significant positive association between poor glycemic control and increased stroke risk, poor glycemic control with a mean HbA1c of 8.89% in a study by Khalid Al-Rubeaan et al., was associated with a nonsignificant increase in the risk of stroke. This observation is supported by the observation among Caucasians that the risk for stroke was nonsignificant with HbA1c < 9%, whereas it was significant with HbA1c > 9%.[14]

In our study, 142 out of 200 patients had RBS<200, of them,74(52.11%) had HbA1c ≥ 6.5%, 58 out of 200 patients had RBS>200, all of them had HbA1c ≥ 6.5%.

In a study by ROBERT A SILVERMAN et al.,there were 541 patients enrolled. Among the 331 patients with a glucose level > or =110 mg/dL, 22.4% had an elevated HbA(1c) level; among the 210 patients with a glucose level < 110 mg/dL, 7.6% had an elevated HbA1c level. There were few patients (n = 13) with a glucose level > or =200 mg/dL, but most (85%) had an elevated

HbA1c level. Among the 140 patients with a mildly elevated glucose level (110-125 mg/dL), 16.4% had an elevated HbA(1c) level.[15]

In a study by Prachand Man Singh Rajbhandari et al., Among 75 patient observed, 18(62.1%) had blood sugar <200 mg/dl and HbA1c <6.3,15(32.6%) had blood sugar <126 mg/dl and HbA1c >6.3, 11(37.9%) had blood sugar >200 mg/ dl and HbA1c <6.3, similarly , 31(67.4%) had blood sugar >200 mg/ dl and HbA1c >6.3.

We also noted that 46(23%) out of 200 patients were diabetics who were on treatment (either with OHA or insulin). In a study by Niaz Ahmed et al., 17% of patients had a history of diabetes, 81.3% had no history of diabetes, and for 1.6% of patients, diabetes was unknown. In a study by SK Marulaiah et al., 27.8% were known diabetic patients.[16] In a study by IYAD ALI et al., 49% of patients had diabetes mellitus.

Our study also noted that RBS was ≥ 200 in only 14 out of 46(30.43%) patients whose diabetic status was known and were on treatment. All these patients(100%) had HBA1C ≥ 6.5% suggesting the high sensitivity of HbA1c. 32 out of 46 patients (69.56%) had RBS in the normal range, but 14(43.75) of them had HbA1C ≥6.5.

In a study by VERANNA MOHAN GADAD et al., 20 out of 50 patients were diabetics who were on treatment (either with OHA or insulin). 19 (95%) of them had HbA1c ≥ 6.5%, and among these, 16 (80%) had HbA1c > 7%.

Among the patients with the glycemic status, notknown 110 of 154 patients (71.4%) had RBS in the normal range, out of which 61 of the 110 (55.45%) had HbA1c in the diabetic range (≥ 6.5%), suggesting the poor sensitivity of RBS in detecting glycemic status. 44 out of 154 patients (28.57%) had RBS > 200mg/dl, all of them had HbA1c at ≥ 6.5%. The difference between RBS and HbA1c was statistically significant, with a P-value of < 0.05.

In a study by VERANNA MOHAN GADAD et al., Among the patients with the glycemic status notknown, 27 of 30 patients (90%) had RBS in the normal range, out of which 15 (55.5%) had HbA1c in the diabetic range (≥ 6.5%) .3 out of 30 patients (10%) had RBS > 200mg/dl, all of them had HbA1c ≥ 6.5%, supporting our study.

CONCLUSION

- Hyperglycemia recognized or unrecognized is a major risk factor for stroke. Lifestyle changes and a targeted poly pharmaceutical treatment strategy can reduce these risks.
- HbA1C may be a better indicator of glycemic status than RBS in stroke.
- Achieving an HbA1C target of less than 7% in diabetic patients is very important to prevent stroke.
- Regular diabetic screening with HbA1c at community level may help in prevention of many diabetic related complications.

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