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Original Research Article

Study of insulin resistance as an inflammatory marker for ischemic stroke severity among non-diabetics

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ABSTRACT

Background: Insulin resistance (IR) is emerging as an important modifiable risk factor causing acute ischemic stroke. The purpose of the study was to evaluate insulin resistance among patients of acute ischemic stroke, in non-diabetic patients, and to correlate insulin resistance with the severity of acute ischemic stroke, and to observe its association with traditional risk factors.
Methods: It was a prospective study conducted at JSS Medical College, Mysore, India from September 2021 to December 2022. Patients who presented with the history of stroke, who were non-diabetics and aged >18 years were included with informed consent. Ischemic stroke was diagnosed with clinical findings and by neuroimaging. Stroke severity was assessed by NIHSS score. Homeostasis model assessment (HOMA) was used to estimate insulin resistance and the levels were studied in relation to the stroke severity.
Results: A total of 127 non-diabetic ischemic stroke patients were enrolled in the study. Hyperinsulinemia, i.e. serum insulin >9 µU/mL, was observed in 44 (34.64%) patients. IR with HOMA-IR ≥2.5 was noted in 39 (30.7%) patients. NIHSS score in severity (group III) was strongly associated with serum insulin >9 µU/mL (62.1%) (P = 0.001) and HOMA-IR ≥2.5 (62.1%) (P<0.0001).
Conclusions: Screening for insulin resistance in nondiabetic patients with ischemic stroke may identify those who are at higher risk for poor outcomes, allowing for early intervention and closer monitoring. Also, interventions to reduce insulin resistance, such as lifestyle modifications or medications, may be beneficial in improving stroke outcomes.

Keywords: HOMA-IR, Insulin resistance, Ischemic stroke, NIHSS, Non-diabetic

INTRODUCTION

Stroke is a global health problem. Despite the successful implementation of preventive measures, it is the second commonest cause of death and the fourth leading cause of disability globally.[1] Ischemic stroke account for 85% of all strokes and hence are an important cause of mortality and morbidity in the community. Developing countries like India are witnessing an increasing incidence of ischemic stroke, especially in the young.

Insulin has been recognized as a neuroprotector. Recent studies have suggested that insulin resistance may play a role in the pathogenesis of ischemic strokes. With the benefits of modification of other risk factors not significantly affecting the incidence, mortality, and morbidity, Insulin resistance is emerging as an important modifiable risk factor causing acute ischemic stroke.

Atherosclerosis Risk in Communities (ARIC) study found an increase in the relative risk for ischemic stroke of 1.19 for every 50 pmol/L increase in basal insulin

among non-diabetics, indicating the role of insulin resistance.[2] Diabetes mellitus with its inherent Insulin resistance is a known risk factor for strokes.[2-5] However, the impact of insulin resistance on ischemic strokes among nondiabetics has not been well studied even in our country. Hence, this study was proposed to evaluate insulin resistance among patients of acute ischemic stroke without past history or lab evidence of diabetes mellitus. In addition, we attempted to correlate IR with the severity of acute ischemic stroke and to observe its association with traditional risk factors.

Insulin protects brain tissue development by preventing ischemia, oxidative stress, and apoptosis-induced brain tissue damage, regulating cholesterol metabolism in neurons and astrocytes. Many epidemiological studies have shown that insulin resistance, plays a critical role in the development of ischemic stroke, possibly through the following mechanisms: i) Acceleration of atherosclerosis by insulin resistance. ii) hemodynamic disturbances. iii) enhanced platelet adhesion, activation, and aggregation. iv) amplification of the role of other risk factors in ischemic stroke.

IR, as the name implies, is the failure of tissues to the normal response to insulin stimulation.[6] IR appears earlier in brain tissue than in the periphery, suggesting that brain tissue is more vulnerable to IR, particularly in brain diseases such as ischemic stroke There are four clinically accepted criteria for detecting the presence of IR in patients: (1) the gold standard assessment, homeostasis model assessment of IR (HOMA-IR); (2) oral glucose tolerance tests (OGTT); (3) C-peptide release test; and (4) triglyceride glucose (TyG) index, each with advantages and disadvantages.[7-10]

There have been studies into the relationship between insulin resistance and ischemic stroke severity among nondiabetic patients. A study by Ribo et al found that insulin resistance was associated with a worse prognosis in non-diabetic patients with acute ischemic stroke.[11] Zhao et al found that insulin resistance was independently associated with the severity of ischemic stroke among nondiabetic patients.[12] In addition, a study by Cai et al found that insulin resistance was associated with poor functional outcomes and a higher risk of recurrent stroke in non-diabetic patients with acute ischemic stroke.[13]

Several studies have explored the potential mechanisms underlying the relationship between insulin resistance and stroke severity. Zhang et al demonstrated that insulin resistance was associated with increased levels of inflammatory markers among patients with acute ischemic stroke, which may have a bearing on the severity.[14] Another potential mechanism is the role of oxidative stress. Insulin resistance has been shown to increase oxidative stress, which has been implicated in the pathogenesis of stroke. In a study by Park et al, insulin resistance was found to be associated with increased oxidative stress in patients with acute ischemic stroke.[15]

Based on such evidence clinical studies have investigated the use of insulin and insulin sensitizers in the treatment of acute ischemic stroke. A pilot clinical trial supports that pioglitazone (insulin sensitizer) is effective in improving outcomes among nondiabetic patients with a recent transient ischemic attack or non-disabling ischemic stroke.[16]

Objectives of the study were to measure the prevalence of IR in non-diabetic ischemic stroke patient, to correlate IR with the ischemic stroke severity (assessed using NIHSS score) and to observe for clustering of the traditional risk factors in them.

METHODS

This study was a hospital-based clinical prospective study, conducted at JSS medical college and hospital, Mysuru, Karnataka, India, over 18 months from September 2021 to December 2022, which included 127 Patients attending the neurology outpatient department, emergency, who presented with a history of acute ischemic stroke, who were nondiabetics and aged >18 years. A standardized, structured interview was conducted and recorded in the proforma after obtaining permission from the institutional ethical committee of JSS Medical College and Hospital. Consent was obtained from all the participants/guardians in the study group. Patients with diabetes (FBS >126 mg% and /or HbA1C >6.4%), age less than 18 years, cortical venous sinus thrombosis, head injury, subdural hematoma, cerebral tumors, hemorrhagic stroke, meningitis, and pre-existing or incidentally detected cardiac disorders were excluded from the study.

Demographic data and risk factors were included. Vitals and anthropometric examination, such as body mass index (BMI) and waist circumference (WC), were calculated. Ischemic stroke was diagnosed with clinical findings and investigations such as brain CT, MRI, echocardiography, and duplex imaging of extracranial arteries. Blood investigations such as fasting blood sugar, fasting serum insulin, HbA1c, and fasting lipid profile were done. Insulin resistance was assessed using the Homeostasis model assessment (HOMA). In this study, the normal insulin value for non-diabetic adults is 0.7-9 μU/mL and values >9 μU/mL were taken as hyperinsulinemia. Insulin resistance was defined as HOMA-IR ≥2.5 which was calculated using the formula {fasting plasma glucose (mg/dl) x fasting plasma insulin (μU/mL)}/405.

The stroke subtypes were based on the classification of subtypes of acute ischemic stroke by the Trial of Org 10172 in Acute Stroke Treatment (TOAST). The severity of the stroke was assessed by National Institutes of Health Stroke Scale (NIHSS). Based on NIHSS score at

admission, patients were divided into three groups: 1) group I-NIHSS score at admission 1-8; 2) group II - NIHSS score at admission 9-18; 3) group III-NIHSS score at admission >18.

Statistical analysis was done by measuring proportions for categorical/binary variables and the chi-square test/fisher exact test was used to compare two or more independent proportions. Fisher exact was used when the number of expected numbers in >25% cells is <5. All the statistical methods were done using SPSS 21.0 version for windows. P value <0.05 was considered statistically significant.

RESULTS

Total 127 subjects who met inclusion criteria were studied. Ages varied from 23 years to 95 years (mean-60 yrs and SD 14yrs). 88 (69.2%) subjects were male and 39 (30.7%) were female. Mean BMI was 29.24kg/m^2 among females and 23.98kg/m^2 among males.

Table 1: Acute ischemic stroke subtypes among various age groups.

Age group	Overall	Male	Female	Large artery atherosclerosis	Small vessel occlusion (lacunar infarcts)
<40	5	1	4	3	2
40-49	20	13	7	11	9
50-59	42	30	12	23	19
60-69	21	19	2	12	9
≥70	39	25	14	22	17
Total	127	88	39	71	56

Table 2: Mean, minimum, maximum, standard deviations of all the parameters.

			Mean	SD	Q1	Q2	Q3	Minimum	Maximum
Age			60	14	50	56	74	23	95
NIHSS			13	8	7	13	17	2	35
Gender	Female	BMI (kg/m^2)	29.24	3.42	26.90	27.90	32.40	23.16	36.60
		waist circumference (cm)	88	5	84	89	92	78	96
	Male	BMI (kg/m^2)	23.98	2.99	22.00	24.10	26.21	18.20	31.45
		waist circumference (cm)	88	5	84	88	92	78	98
FBS (mg/dl)			93	13	85	95	101	64	120
HbA1c			5.47	.41	5.10	5.40	5.90	4.80	6.40
Total Chol (mg/dl)			184	21	167	184	201	140	236
LDL (mg/dl)			90	16	77	88	102	60	121
TGL (mg/dl)			156	27	135	145	178	112	222
S. insulin (µU/ml)			9.66	5.07	6.20	8.10	13.00	1.80	22.40
HOMA-IR			2.307	1.393	1.390	1.910	3.340	.330	6.410

The stroke subtypes according to TOAST classification were 1) atherothrombotic infarction (large-artery atherosclerosis) (n = 71); 2) Lacunar infarction (small-artery occlusion) (n = 56) and 3) cardioembolism (n = 0). Stroke subtypes among various age groups mentioned in Table 1. Among the subjects mean FBS and HbA1C were 93 (mg/dl) and 5.47 respectively, whereas mean s insulin (range 1.80µU/ml-22.4µU/ml) and HOMA-IR (range 0.33 -6.41) among the study group were 9.66 (µU/ml) and 2.307 respectively. Mean, minimum, maximum and standard deviations of various parameters mentioned in Table 2.

Hypertension was detected among 72 subjects (56.69%). Alcohol consumption and smoking were seen only in males in our study. Among males, 35 (39.77%) were alcoholics and 34 (38.63%) were smokers. Total 99 subjects (77.95%) had BMI ≥23. Waist circumference of ≥90 cm was observed in 34 males (38.6%) and 36 females (92.3%) had WC ≥80 cm. Lipid profile analysis revealed that 37 patients (29.1%) had total cholesterol ≥200 mg/dL, 34 patients (26.77%) had LDL >100 mg/dL, and 58 (46.09%) patients had triglycerides ≥150 mg/dL. Hyperinsulinemia, i.e. serum insulin >9 µU/mL, was observed in 44 (34.64%) patients. IR with HOMA-IR ≥2.5 was noted in 39 (30.7%) patients. Patients with NIHSS score 1-8 were 46 (36.22%), NIHSS score 9-18 were 52 (40.94%), and NIHSS score >18 were 29 (22.83%). Subjects with high NIHSS score had large

artery atherosclerosis while majority of subjects with low NIHSS score had small vessel occlusion (Table 3).

Table 3: Stroke subtypes among subjects with insulin resistance.

Total patients with HOMA-IR ≥2.5 are 39				
		NIHSS 1-8 (Group-I)	NIHSS 9-18 (Group-II)	NIHSS > 18 (Group-III)
Large artery atherosclerosis	22	2	6	14
Small vessel occlusion (lacunar infarcts)	17	9	5	3

Table 4: Comparison of demographic, anthropometric and biochemical parameters in relation to stroke severity.

				NIHSS at admission						
				Group I (1-8)		II (9-18)		Group III (>18)		P value
				n	%	n	%	n	%	
Age group	<40			2	4.3	3	5.8	0	0.0	0.7
	40-49			7	15.2	7	13.5	6	20.7	
	50-59			13	28.3	17	32.7	12	41.4	
	60-69			10	21.7	9	17.3	2	6.9	
	>=70			14	30.4	16	30.8	9	31.0	
Gender	Female			12	26.1	12	23.1	15	51.7	0.02
	Male			34	73.9	40	76.9	14	48.3	
Gender	Female	Waist circumference (cm)	<80	1	8.3	2	16.7	0	0.0	0.3
			≥80	11	91.7	10	83.3	15	100.0	
	Male	Waist circumference (cm)	<90	20	58.8	26	65.0	8	57.1	0.8
			≥90	14	41.2	14	35.0	6	42.9	
BMI	<23 kg/m^2			13	28.3	13	25	2	6.9	0.08
	≥ 23 kg/m^2			33	71.7	39	75	27	93.1	
Alcoholic	No			32	69.6	37	71.2	23	79.3	0.6
	Yes			14	30.4	15	28.8	6	20.7	
Smoker	No			30	65.2	36	69.2	27	93.1	0.2
	Yes			16	34.8	16	30.8	2	6.9	
HTN	No			24	52.2	22	42.3	9	31.0	0.2
	Yes			22	47.8	30	57.7	20	69.0	
Total Chol (mg/dl)	<200 mg/dl			39	84.8	37	71.2	14	48.3	0.003
	≥200 mg/dl			7	15.2	15	28.8	15	51.7	
LDL(mg/dl)	<100 mg/dl			35	76.1	41	78.8	17	58.6	0.123
	≥100 mg/dl			11	23.9	11	21.2	12	41.4	
TGL(mg/dl)	<150			28	60.9	24	46.2	17	58.6	0.3
	≥150			18	39.1	28	53.8	12	41.4	

Of the 29 subjects with severe stroke (NIHSS >18) at presentation, 15 were females. This group had 27 patients with a BMI ≥23 (Table 4).

In addition 18 patients had insulin resistance (HOMA-IR ≥2.5) and elevated Insulin levels >9 µU/mL. These associations were statistically significant (Table 5 and 6).

The 62.1 in group III had FBS 101-125 mg/dl (p<0.0001), while 84.8% and 76.9% in groups I and II respectively had FBS ≤100 mg/dl (p<0.0001) (Table 7).

Total 58.6% in group III had HbA1C 5.7-6.4 (p=0.002), while 80.4% and 59.6% in group I and II respectively had HbA1C ≤5.6 (p=0.002) (Table 8).

Table 5: Comparison of HOMA-IR in relation to stroke severity.

		NIHSS at admission						
		Group I (1-8)		II (9-18)		Group III(>18)		P value
HOMA-IR	<1	14	30.4%	2	3.8%	0	0.0%	<0.0001

Continued.

		NIHSS at admission						
		Group I (1-8)		II (9-18)		Group III(>18)		P value
	1-1.5	14	30.4%	10	19.2%	2	6.9%	
	1.5-2	7	15.2%	17	32.7%	5	17.2%	
	2-2.5	4	8.7%	9	17.3%	4	13.8%	
	≥2.5	7	15.2%	14	26.9%	18	62.1%	

Table 6: Comparison of serum insulin in relation to stroke severity.

		NIHSS at admission						
		Group I (1-8)		II (9-18)		Group III(>18)		P value
S. insulin (µU/ml)	≤9	37	80.4%	35	67.3%	11	37.9%	0.001
	>9	9	19.6%	17	32.7%	18	62.1%	

Table 7: Comparison of FBS in relation to stroke severity.

		NIHSS at admission						
		Group I (1-8)		II (9-18)		Group III(>18)		P value
FBS (mg/dl)	≤100mg/dl	39	84.8%	40	76.9%	11	37.9%	<0.0001
	101-125 mg/dl	7	15.2%	12	23.1%	18	62.1%	

Table 8: Comparison of HbA1C in relation to stroke severity.

		NIHSS at admission						
		Group I (1-8)		II (9-18)		Group III (>18)		P value
HbA1c	≤5.6%	37	80.4%	31	59.6%	12	41.4%	0.002
	5.7-6.4%	9	19.6%	21	40.4%	17	58.6%	

DISCUSSION

In this study, we investigated the relationship between insulin resistance and ischemic stroke severity among nondiabetic patients. Our findings suggest that insulin resistance may serve as a marker for severity of ischemic stroke.

This study demonstrated a positive relationship between HOMA-IR and ischemic stroke severity among non-diabetic patients adjusting for traditional risk factors for stroke. Similar results were noted by Rundek in the western population and Nakamura et al. in Asians and in Bruneck study.[17-19] We found that higher levels of insulin resistance were associated with increased stroke severity. This was consistent with the findings of Yang et al. It has been postulated that IR is associated with increased inflammation and/or oxidative stress which leads to poor functional outcomes.[20]

The majority of studies on IR and stroke were in the age group of 35-68 years in ARIC and Northern Manhattan Study, where as it was 23-95 years in our study.[2,4] Unlike the earlier Northern Manhattan study, males outnumbered females in this study. The majority of the patients were with NIHSS score of 9-18. High serum insulin >9 µU/mL and high HOMA-IR ≥2.5 were strongly associated with high NIHSS score >18, with corresponding P values of 0.001 and <0.0001, respectively.

Olijhoek et al noted in their study that 43% of patients with acute ischemic stroke had components of metabolic syndrome.[21] Author noted increased waist circumference in 55.1%, increased triglycerides in 45.66% and hypertension in 56.69% of in this subjects.

Most of our patients had a NIHSS score between 9-18. NIHSS scores >18 were associated with high serum insulin >9 µU/mL (p=0.001) and HOMA-IR ≥2.5 (p<0.0001). In contrast, Yuen et al and Wang et al could not find any relation with stroke severity or functional outcome with IR in their studies.[22,23] However, they demonstrated that insulin resistance was independently associated with an increased risk of recurrent stroke and cardiovascular events during follow-up. Since ours is a cross-sectional study we are unable to comment on this aspect. In contrast to these studies, Renske et al found no association between IR and risk of stroke or the stroke subtypes.[24] Furthermore, multicentered prospective trials can throw more light on this novel risk factor of stroke.

The study was conducted in a single centre and included a relatively small sample size. As a result, the findings may not be generalizable to other populations or settings. The study relied on a single measurement of insulin

resistance (i.e., HOMA-IR index) and did not account for changes in insulin resistance over time. Also, lack of follow up of these patients deprives us the data about stroke recurrence and other cardiovascular events at follow up. This may limit the accuracy of the findings and the ability to draw causal inferences. The study did not assess the potential confounding effects of other factors that may contribute to stroke severity, such as age, comorbidities, or medication use.

CONCLUSION

To conclude, screening for insulin resistance in non-diabetic patients with ischemic stroke may identify those who are at higher risk for poor outcomes, allowing for early intervention and closer monitoring. Also, interventions to reduce insulin resistance, such as lifestyle modifications or medications, may be beneficial in improving stroke outcomes. Future research is needed to confirm our findings and explore potential interventions to reduce insulin resistance and improve outcomes in this group.

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