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ORIGINAL RESEARCH

A Prospective Study of the Prevalence of Insulin Resistance in Ischemic Stroke And its Correlation with the Traditional Risk Factors for Stroke in Eastern India

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Abstract

Background: In this study, we wanted to evaluate the prevalence of insulin resistance in ischemic stroke (IS) by using a homeostasis model assessment for insulin resistance (IR).

Methods: This was a hospital-based cross-sectional analytical study conducted among 100 patients who presented with acute ischemic stroke to the Department of General Medicine and Neurology, Sriram Chandra Bhanja Medical College & Hospital (SCBMCH), Cuttack, Odisha from September 2020 to August 2021. The study was conducted after obtaining clearance from the institutional ethics committee (IEC) and written informed consent from the study participants.

Results: The range of FBS, PPBS, Fasting Plasma Insulin (FPI) and HbA1c in the study population was 77-164, 119-240, 4.2-12.9 and 4.3-7.1 respectively. High prevalence of Abnormal Glucose Metabolism (AGM) expressed as Impaired Glucose tolerance (IGT) and Diabetes mellitus (DM) was observed in patients with ischemic stroke (60%), out of which 38 with IGT and 22 with DM. The mean systolic and diastolic blood pressure in the study population was expressed in mean ± SD in which 73 (73%) cases were hypertensive while 27 (27%) were not hypertensive. The distribution of cases according to the presence of dyslipidaemia, history of smoking and presence of atrial fibrillation (AF) on ECG was 46 (46%), 21 (21%) and 11 (11%) respectively. The distribution of subtypes of ischemic stroke was according to the presence of AF on ECG. Only patients with cardio-embolic (CE) stroke showed AF on ECG with a statistically significant difference between the three of the Atherothrombotic infarct (ATI), Cardio-embolic (CE), Lacunar Infarct (LI) subgroups ($p < 0.001$). Hypertension, dyslipidaemia, and smoking were positively correlated with Insulin Resistance with p-value <0.01, <0.01 and 0.012 respectively.

Conclusion: The frequency of ischemic stroke is more among older individuals (age > 55 years), suggesting that age is an independent risk factor for stroke. Hypertension and dyslipidaemia are the two most common modifiable risk factors for ischemic stroke,

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particularly in patients with atherothrombotic and lacunar infarction. Insulin resistance and abnormal glucose metabolism are common in acute ischemic stroke patients with no history of diabetes. IGT and Insulin resistance correlated significantly with pathogenic factors underlying the development of ischemic stroke. Insulin resistance can modify and influence the role of modifiable risk factors in patients with ischemic stroke.

Keywords: Insulin resistance, ischemic stroke, correlation, risk factors.

Introduction

According to a definition proposed by the World Health Organization (WHO) in 1970, "stroke is rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer, or leading to death, with no apparent cause other than of vascular origin."[1] The definition of stroke recently proposed by the American Stroke Association also includes clinical and tissue criteria in which it is depicted as "any objective evidence of permanent brain, spinal cord or retinal cell death attributed to a vascular aetiology based on pathological or imaging evidence with or without the presence of clinical symptoms."[2] Stroke has been placed as a priority public health burden, which is poised to rise over future decades because of the demographic transition of population, particularly in developing countries.[3] The burden of stroke is increasing, the reason being changing lifestyles, increasing longevity, and smoking. Besides this, there are other known risk factors for stroke which include diabetes mellitus (DM), hypertension, dyslipidaemia, obesity and metabolic syndrome which are also on the rise. In contrast to developed countries where the incidence of stroke has been decreasing or reached a plateau, the burden of stroke has been increasing in developing countries in the last few decades, particularly in India. The rise in stroke burden in India like other developing countries may be due to increasing longevity, lifestyle changes, smoking and accompanying urbanization. Indians may also be genetically prone to stroke due to the high prevalence of metabolic syndrome consisting of central obesity, high levels of triglyceride, and low levels of HDL cholesterol with or without impaired glucose tolerance (IGT). Stroke is classified into two major categories, ischemic stroke (IS) and haemorrhagic stroke. The Indian Collaborative Acute Stroke Study (ICASS) reported that 77% of total strokes were of ischemic type.[4] The ICMR has observed that hypertension, DM, tobacco use and low haemoglobin are important risk factors for IS. DM doubles the risk of IS and worsens the survival of patients with acute stroke. However, the onset of diabetes may occur several years before the clinical diagnosis and its development is preceded by a prolonged period of insulin resistance (IR). Hyperglycaemia during the acute phase of stroke occurs in about one-third of patients without a prior diagnosis of diabetes and is associated with adverse neurological outcomes and increased stroke mortality.[5]

The critical role of IR in the pathogenesis of IS is increasing. IR often refers to a pathological condition in which cells fail to respond to the normal actions of insulin. It plays an important role in the pathogenesis of IS by accelerating the march towards atherosclerosis. Literature review indicates that IR enhances platelet adhesion, platelet activation and aggregation which are conducive to the occurrence of IS.[6] IR also induces hemodynamic disturbances and contributes to the onset of IS. In addition, IR may augment the role of the modifiable risk factors in IS and induce the occurrence of IS. From the point of view of indirect prevention of stroke, it is important to evaluate the exact prevalence of IR in patients with IS. Previous studies demonstrated a high prevalence of abnormal glucose metabolism (AGM) including IGT in European, American and Chinese stroke patients based on the result of the oral glucose tolerance test (OGTT).[7] However, there are sparse reports assessing the prevalence of IR in IS in Indian patients with previously undiagnosed DM.

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Aims and objectives

- To assess the prevalence of insulin resistance in ischemic stroke patients with no history of diabetes.
- To find the correlation between insulin resistance and the traditional risk factors for stroke.

Methods

This was a hospital-based cross-sectional analytical study conducted among 100 patients who presented with acute ischemic stroke (IS) to the Department of General Medicine and Neurology, SCBMCH, Cuttack, Odisha from September 2020 to August 2021. The study was conducted after obtaining clearance from the institutional ethics committee (IEC Appln. No. 283/dated 26.08.2020) and written informed consent from the study participants.

Inclusion criteria

- Patients diagnosed to have an ischemic stroke (Embolic, thrombotic or stenosis) with a new focal neurological deficit.
- Admitted within 7 days of symptom onset, with a corresponding lesion on computed tomography (CT) scan.
- Magnetic Resonance Imaging (MRI) with no history of diabetes.

Exclusion criteria

- Strokes with haemorrhagic lesions on CT or MRI.
- Patients with a known case of type 2 DM (either self-reported physician diagnosis of DM or on hypoglycaemic medications (e.g., insulin or oral hypoglycaemic agents) before hospitalization.

Statistical methods

- All observational data were statistically analysed to conclude.
- Statistical analysis was done using SPSS package version 20.0.
- Quantitative variables were described as mean ± standard definition unless otherwise indicated.
- Qualitative variables were described by percentage.
- Pearson's correlation coefficient, logistic regression analysis, and multivariate analysis were used.
- 'P' value <0.05 was considered to be significant.

Results

Clinical Presentation	**No. of Cases (%)**
Altered Sensorium	15 (15.0)
Convulsions	6 (6.0)
Left-sided weakness	22 (22.0)
Loss of Speech	4 (4.0)
Right-sided weakness	53 (53.0)
Distribution of cases according to the clinical presentation. (N = 100)	
Fasting Blood Sugar (mg/dL**)**	**No. of Cases (%)**
Less than 100 mg/dL (NGT)	40 (40.0)
100 – 126 mg/dL (IFG)	38 (38.0)
More than 126 mg/dL (DM)	22 (22.0)
Distribution of cases according to abnormal glucose metabolism. (N = 100)	

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Parameter	Mean (SD)	Range
FBS (mg/dL)	110.42 (19.96)	77 – 164
FBS (mmol/L)	6.13 (1.11)	4.30 – 9.10
PPBS (mg/dL)	157.88 (33.81)	119 – 240
FPI (mIU/L)	7.47 (1.63)	4.2 – 12.9
HbA1c	5.45 (0.53)	4.3 – 7.1
Mean blood glucose values for the study population. (N = 100)		
Table 1		

High prevalence of AGM (IGT and DM) was observed in patients with IS (60%), out of which 38 with IGT and 22 with DM. The mean blood glucose values for the study population are expressed in mean ± SD. The range of FBS, PPBS, FPI and HbA1c in the study population was 77-164, 119-240, 4.2-12.9 and 4.3-7.1 respectively.

Parameter	Mean (SD)	Range
HOMA-IR	2.01 (0.57)	1.1 – 4.4
Categories (HOMA-IR)	**No. of Cases (%)**	
Normal	43 (43.0)	
Insulin Resistance (IR)	57 (57.0)	
Distribution of cases according to homeostasis model assessment. (N =- 100)		
Parameters	**Mean (SD)**	**Range**
Systolic Blood Pressure	141.32 (10.95)	112 – 160
Diastolic Blood Pressure	90.20 (8.95)	70 – 112
Hypertension	**No. of Cases (%)**	
Hypertensive	73 (73.0)	
Not Hypertensive	27 (27.0)	
Mean systolic and diastolic blood pressure for the study population. (N = 100)		
Parameters	**Mean (SD)**	**Range**
HDL (mg/dL)	46.88 (4.67)	35 – 59
LDL (mg/dL)	118.14 (21.27)	81 – 157
Total Cholesterol (mg/dL)	184.43 (22.03)	139 – 262
Triglycerides (mg/dL)	125.56 (22.14)	84 – 177
Lipid profile of the study population. (N = 100)		
Table 2		

The prevalence of IR in IS was high (57%). The value of HOMA ranged from 1.1 to 4.4 in the study group. The mean systolic and diastolic blood pressure in the study population is in mean±SD. 73 (73%) cases were hypertensive while 27 (27%) were not hypertensive. The lipid profile values in the study population are in mean±SD. The values of HDL, LDL, total cholesterol (TC), and triglycerides ranged from 35-59, 81-157, 139-262. 84-177 mg/dl respectively.

Dyslipidaemia	No. of Cases (%)
Present	46 (46.0)
Absent	54 (54.0)
Distribution of cases according to the presence of dyslipidaemia. (N = 100)	
History of Smoking	**No. of Cases (%)**
Present	21 (21.0)
Absent	79 (79.0)
Distribution of cases according to the presence of history of smoking. (N = 100)	
Atrial Fibrillation (on ECG)	**No. of Cases (%)**
Present	11 (11.0)

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Absent	89 (89.0)
Distribution of cases according to the presence of atrial fibrillation on ECG. (N = 100)	
Table 3	

The distribution of cases according to the presence of dyslipidaemia, history of smoking and presence of AF on ECG were 46 (46%), 21 (21%) and 11 (11%) respectively.

Sex	**ATI**	**CE**	**LI**
Male	30	6	16
Female	32	5	11
p-value = 0.635			
Distribution of subtypes of ischemic stroke according to the sex of the patient. (N = 100)			
FBS/PPBS	**ATI (%)**	**CE (%)**	**LI (%)**
NGT	29 (46.7)	6 (54.5)	7 (25.9)
IFG/IGT	22 (35.4)	4 (36.3)	10 (37.03)
DM	11 (17.7)	1 (9.09)	10 (37.03)
p-value = 0.129			
Distribution of subtypes of ischemic stroke according to blood glucose. (N = 100)			
	The subtype of ischemic stroke		
	ATI (%)	**CE (%)**	**LI (%)**
Normal Glucose Metabolism	29 (46.8)	6(54.6)	7 (25.9)
Abnormal Glucose Metabolism (IGT & DM)	33 (53.2)	5 (45.4)	20 (74.1)
Distribution of cases with AGM according to subtypes of ischemic stroke			
Table 4			

Among the subtypes of IS, the incidence of ATI was highest in both males and females. In the distribution of subtypes of IS according to blood glucose, the number of cases with IGT was more in patients with Atherothrombotic infarct (ATI) compared to Cardio-embolic (CE) and Lacunar Infarct (LI) while DM was present in an equal number of cases with ATI and LI. But the percentage of cases with IGT and DM was more in LI cases compared to the other two groups. In the distribution of cases with AGM according to subtypes of IS, the prevalence of AGM was more in patients with LI i.e., 74.1% compared to ATI (53.2%) and CE (45.4%).

HOMA	**ATI**	**CE**	**LI**
Normal	24	11	8
Insulin Resistance	38 (61.2%)	0	19 (70.3%)
p-value = <0.001			
Distribution of subtypes of ischemic stroke according to insulin resistance on homeostasis model assessment. (n = 100)			
Hypertension	**ATI**	**CE**	**LI**
Present	41(66.1%)	9 (81.8%)	23 (85.1%)
Absent	21	2	4
p-value = 0.148			
Distribution of subtypes of ischemic stroke according to hypertension. (N = 100)			
Dyslipidaemia	**ATI**	**CE**	**LI**
Present	30 (48.3%)	5 (45.4%)	11 (40.7%)
Absent	32	6	16
p-value = 0.873			
Distribution of subtypes of ischemic stroke according to the presence of dyslipidaemia (N = 100)			

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History of Smoking	ATI	CE	LI
Present	12 (19.3%)	2 (18.1%)	7 (25.9%)
Absent	50	9	20
p-value = 0.765			
Distribution of subtypes of ischemic stroke according to the history of smoking. (N = 100)			
Table 5			

In the distribution of subtypes of IS according to IR on HOMA, 57 (57%) patients showed IR out of which 38 (66.6%) and 19 (33.3%) cases were in ATI and LI groups respectively. Patients with CE did not show IR. In the distribution of subtypes of IS according to the presence of hypertension, dyslipidaemia and history of smoking, the number of cases with hypertension, dyslipidaemia and a history of smoking was more in patients with ATI compared to the other two groups. But the incidence of hypertension and smoking was more in cases with LI (85.1% & 25.9% respectively) than in ATI and CE. However, there was no statistically significant difference between the three subgroups.

Atrial fibrillation (on ECG)	ATI	CE	Li
Present	0	11	0
Absent	62	0	27
p-value = <0.001			
Distribution of subtypes of ischemic stroke according to the presence of atrial fibrillation (on ECG). (n = 100)			
Patient characteristics	**Correlation score**		**p-value**
Age	0.137		0.528
Sex	0.172		0.291
Hypertension	0.649		<0.01
Dyslipidaemia	0.513		<0.01
Smoking	0.431		0.012
Atrial fibrillation (on ECG)	0.008		<0.001
Correlation of insulin resistance with patient characteristics. (n = 100)			
Table 6			

In the distribution of subtypes of IS according to the presence of AF on ECG, only patients with CE showed AF on ECG with a statistically significant difference between the three subgroups ($p<0.001$). The correlation of IR with patient characteristics showed that hypertension, dyslipidaemia, and smoking were positively correlated with IR with p values <0.01, <0.01 and 0.012 respectively. The correlation of IR could not be described with age, sex and AF.

Discussion

Distribution of cases according to the presence of risk factors

In our study, common vascular risk factors were hypertension (n=73, 73%), dyslipidaemia (n=46, 46%), smoking (n=21, 21%), and AF (n=11, 11%). The higher the blood pressure, the greater the stroke risk (Lewington et al. 2002).[8] In the present study, hypertension was the most common risk factor for IS. Its prevalence showed no significant difference between two gender groups or in all age groups. The frequency of stroke was more in our study in hypertensive patients as compared to non-hypertensive patients. This finding can be explained by the fact that hypertension is associated with atherosclerosis and it further accelerates the atherogenic process leading to large vessel atherothrombosis, vessel stenosis and occlusion due to thrombus formation and artery-to-artery embolism.

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Hypertension as a risk was present in 73% of our cases (Table-2) which was greater than 61% and 60% reported by Basharat et al (2002) [9] and Miller J et al (2014) respectively.[10] Chobanian et al (2003)[11] reported that control of high blood pressure contributes to the prevention of stroke as well as the prevention or reduction of other target organ damage, including congestive heart failure and renal failure.

The percentage of dyslipidemic individuals among the study population amounted to 46% (Table-3), hence showing a positive correlation between dyslipidaemia and stroke. The pattern of dyslipidaemia showed that 45% of the patients with abnormal lipid profiles had an elevated LDL, 30% had elevated serum TC and only 10% had elevated triglyceride. The values of HDL, LDL, TC and triglycerides ranged from 35-59, 81-157, 139-262, and 84-177 mg/dl respectively.

The Asia Pacific Cohort studies Collaboration found a 25% increase in IS rates for every 1 mmol/L increase in TC described by Zhang et al (2003)[12]. 15% of patients had low HDL, thereby showing a unique correlation between stroke and low HDL level. This finding is consistent with other studies. Our study also showed a preponderance of males among the study population thus reflecting an overall male sex predisposition to stroke. This corroborated a study done by Jishi AA Al et al [13] on profiles of stroke in Bahrain in 2000.

Cigarette smoking is a potent risk factor for stroke as reported by Wolf PA et al 1988 [14] and Markidian J et al 2018[15]. Our present study recorded 21% of male patients with history of smoking as compared to 53% reported by Basharat et al (2002) [9] and 37 % as reported by Bonita R et al. (1986) [16]. It has been proposed that tobacco smoke may increase the risk of IS by inducing a strong inflammatory response.[17] The high frequency of smoking in the present study could be due to low socioeconomic status of the patients and they are more likely to be smokers as they adopt it as a leisure activity and are less likely to stop because of lack of proper awareness.

In concordance with other study results, [18,19,20] we observed a higher incidence of AF in females (75%) than in males; moreover, AF was far more common in patients over 80 years than those under the age of 50 years. As reported by Framingham Heart Study and other related studies, women were more susceptible to AF, [21, 22] thus taking a higher risk for cardiogenic embolism. To be more specific, Roquer et al.[23] figured out through their work that the risk of cardiogenic embolism in women was twice as much as that in men.

The progressive loss of conduction tissue cells and pacemaker function accounts for the increased incidence of AF in the elderly.[24] The higher prevalence of AF and heart diseases in elderly patients, makes cardiogenic embolism a more frequent cause of IS.[25] Some studies suggested that AF might supersede hypertension to be the primary risk factor for IS in patients aged over 80 years.[26]

In the present study, we assessed the prevalence of disorders of glucose metabolism and IR by IGT and HOMA-IR respectively. We studied 100 patients of IS with a mean age of 61.92±11.98 years. Hypertension, dyslipidaemia, smoking, and AF were observed in 73%, 46%, 21% & 11% respectively.

Distribution of cases according to abnormal glucose metabolism (AGM)

Our study demonstrated a high prevalence of AGM in patients with ischemic stroke as was previously reported by Urabe T et al. 2008,[7] 60 (60%) had AGM (FBS>110 mg/dl and 2-hour PPBS>140 mg/dl) including 38 patients with IGT (38%) and 22 with DM (22%). Rest 40 patients (40%) had NGT (FBS<110 mg/dl and 2-hour PPBS<140 mg/dl). The values of FBS and PPBS ranged from 77-164 and 119-240 mg/dl respectively while the HbA1c percentage ranged from 4.3-7.1.

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Association of ischemic stroke (IS) types with patient characteristics

The incidence of ATI was highest in the study group (62%) followed by LI (27%) and CE (11%) as demonstrated in a similar study by Urabe T et al. 2008.[7] The prevalence of abnormal glucose metabolism (IGT and DM) was more in patients with LI i.e., 74.1% compared to ATI (53.2%) and CE (45.4%). In the three subgroups, incidence of ATI was highest in both males and females. The number of cases with IGT was more in ATI cases compared to CE and LI while DM was present equally in both ATI and LI. However, the incidence of DM was high in patients with LI (37.03%) compared to ATI (17.7%). The prevalence of IR was 57% in the study population out of which 38 (61.2%) and 19 (70.3%) cases were in ATI and LI respectively with a statistically significant difference ($p<0.001$). CE cases did not show IR similar to the study by Urabe T et al. 2008.[7] The number of cases with hypertension, dyslipidaemia and a history of smoking was more in patients with ATI compared to the other two subgroups. But the incidence of hypertension and smoking was highest in LI cases (85.1% and 25.9% respectively) within the study group. There was no statistically significant difference in the three subtypes of IS according to the presence of hypertension, dyslipidaemia and history of smoking. Only CE cases showed AF on ECG with a statistically significant difference in the three subgroups ($p<0.001$).

Correlation of insulin resistance with patient characteristics

Hypertension, dyslipidaemia and smoking were positively correlated with IR with 'R'value and 'p'value 0.649 & <0.01, 0.513 & <0.01 and 0.431 & 0.012 respectively. The correlation of IR could not be described with age, sex and AF. Previous studies showed that IR was associated with hyperinsulinemia in Japanese patients with ATI.[27] Although IR seems to be related to hypertension and dyslipidaemia, [29] Masumoto et al [30] evaluated the correlation between IR and classic risk factors in type 2 DM patients. In their results, hyperinsulinemia as a surrogate marker for IR, was a risk factor for stroke. Thus, it was proposed that IR predisposes patients with type 2 DM to IS. In the present study, we evaluated IR by calculating HOMA-IR. Our results showed significantly higher HOMA-IR in ATI and LI patients, although this tendency could not be confirmed in patients with CE. Using the cut-off value for IR from HOMA-IR index ≥ 2.0,[31] 57 (57%) patients developed IR out of which 38 and 19 were in the ATI and LI groups respectively. It was concluded that IR can modify and influence the role of modifiable risk factors in patients with IS. This data suggest that IR seems to be an important risk factor for stroke. All of these studies described a higher prevalence of glucose abnormality in ATI and LI patients with previously undiagnosed DM than in those with other types of IS similar to a study by Urabe T et al. 2008[7] in which ATI cases showed the highest prevalence of AGM. A cohort study in Finland by Kaarisalo MM et al 2006[28] indicated that IGT, is a risk factor for stroke. Our study showed a higher prevalence of IR and IGT than DM, and such prevalence was common in patients with ATI & LI among the subtypes of IS similar to the study by Urabe T et al. (2008).[7] Moreover, previous studies demonstrated that IR accelerates the atherosclerotic process of large cerebral arteries and carotid arteries, resulting in ATI. In our patients, IGT was diagnosed in 36% of IS and 57% of patients developed IR. These results support the tight link between IR and the progression of atherosclerosis. Considered together, these studies and our results suggest that screening for AGM and IR is important for the secondary prevention of stroke.

Conclusion

The frequency of IS is more among older individuals (age > 55 years) suggesting that age is an independent risk factor for stroke. Hypertension and dyslipidaemia are the two most common modifiable risk factors for IS, particularly in patients with ATI and LI. IR and AGM

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are common in acute IS patients with no history of DM. IGT and IR correlated significantly with pathogenic factors underlying the development of IS. IR can modify and influence the role of modifiable risk factors in patients with IS.

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