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Insulin Resistance as an Inflammatory Marker for Ischemic Stroke Severity Among Non-Diabetics: A Prospective Study

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Abstract

Background: Insulin resistance (IR) is one of the inflammatory markers that is receiving increasing attention as a possible early marker of increased risk of cerebrovascular disease. The purpose of the study was to determine the prevalence of IR in non-diabetic ischemic stroke patients and its correlation with the stroke severity.

Methods: It was a prospective study conducted at Narayana Medical College, Nellore from January 2013 to June 2014. After the approval from the institutional ethical committee, 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. Severity of stroke was assessed by National Institutes of Health Stroke Scale (NIHSS) score. Homeostasis model assessment (HOMA) was used to estimate IR and the levels were studied in relation to the stroke severity.

Results: A total of 162 non-diabetic ischemic stroke patients were enrolled in the study. Hyperinsulinemia, i.e., serum insulin > 9 µU/mL, was observed in 41 (25.30%) patients. IR with HOMA-IR ≥ 2.5 was noted in 31 (19.13%) patients. NIHSS score in severity (group III) was strongly associated with serum insulin > 9 µU/mL (54.5%) (P = 0.002) and HOMA-IR ≥ 2.5 (54.5%) (P < 0.0001).

Conclusions: IR may be a novel therapeutic target for stroke prevention. High HOMA-IR was associated with high NIHSS score and it is a useful index for prediction of ischemic stroke in non-diabetics.

Keywords: Cerebral infarction; Stroke; Diabetes; Adults; Computerized tomography; Risk factors

Introduction

Stroke is a global health problem. It is the second commonest cause of death and fourth leading cause of disability worldwide [1]. There is growing evidence about the role of inflammatory mechanism in the pathophysiology of cerebrovascular disease. A diversity of inflammatory markers have been investigated for association with atherosclerosis and cerebrovascular disease, such as fibrinogen, homocysteine, C-reactive protein (CRP), etc., of which insulin resistance (IR) is the one that is receiving increasing attention as a possible early marker for increased risk.

IR is defined as a metabolic state in which a normal concentration of insulin produces less than normal biological response. It has been assigned a central place in metabolic disturbances associated with type 2 DM and obesity [2, 3]. The prevalence of IR is on the rise because of lifestyle modifications. IR is one of the modifiable risk factors causing stroke that is responsible for mortality and morbidity in Asian countries, mostly in young. Several studies have evaluated whether an analogous relationship exists between IR and stroke. Atherosclerosis Risk in Communities (ARIC) study found increased relative risk for ischemic stroke of 1.19 for every 50 pmol/L increase in basal insulin among non-diabetics, supporting role for IR [4]. Though IR is well known to cause ischemic strokes in diabetics [4-7], there are limited data in non-diabetics, from Indian subcontinent. Hence, this study was undertaken to evaluate IR in ischemic stroke patients among non-diabetics.

The aims of the study were to measure the prevalence of IR in non-diabetic ischemic stroke patients, to correlate IR with the ischemic stroke severity, and to observe for clustering of the traditional risk factors in them.

Materials and Methods

Study design

This was a descriptive study done in spanning a period of 1.5 years from January 2013 to June 2014.

Inclusion criteria

Patients attending neurology outpatient department, emergency who presented with the history of stroke, who were non-diabetics and aged > 18 years were included with informed

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Table 1. Comparison of Demographic, Anthropometric and Biochemical Parameters in Relation to Stroke Severity

Parameter	Category	NIHSS at admission			
		Group I (1 - 8)	Group II (9 - 18)	Group III (> 18)	P value
Gender	M (%)	45 (72.6%)	55 (70.5%)	16 (72.7%)	0.95
	F (%)	17 (27.4%)	23 (29.5%)	6 (27.3%)	
	40 - 49 years	19 (30.6%)	15 (19.2 %)	2 (9.1%)	
	50 - 59 years	22 (35.5%)	27 (34.6%)	8 (36.4%)	
	60 - 69 years	12 (19.4%)	18 (23.1%)	7 (31.8%)	
	> 70 years	4 (6.5%)	12 (15.4%)	3 (13.6 %)	
BMI (kg/m^2)	< 23	8 (12.9%)	17 (21.8%)	5 (22.7%)	0.34
	≥ 23	54 (87.1%)	61 (78.2%)	17 (77.3%)	
WC (cm)	M < 90	20 (37.7%)	22 (41.5%)	11 (20.8%)	0.12
	M ≥ 90	25 (39.7%)	33 (52.4%)	5 (7.9%)	
	F < 80	7 (46.7%)	7 (46.7%)	1 (6.7%)	0.51
	F ≥ 80	10 (32.3%)	16 (51.6%)	5 (16.1%)	
HTN	Yes (%)	34 (54.8%)	50 (64.1 %)	14 (63.6%)	0.51
	No (%)	28 (45.2 %)	28 (35.9 %)	8 (36.4 %)	
	No (%)	36 (58.8 %)	48 (61.5 %)	14 (63.6 %)	
T.CHO (mg/dL)	< 200	40 (64.5 %)	46 (59.0 %)	12 (54.5 %)	0.66
	≥ 200	22 (35.5 %)	32 (41.0 %)	10 (45.5 %)	
LDL (mg/dL)	≤ 100	24 (38.7%)	21 (26.9%)	11 (50.0%)	0.09
	> 100	38 (61.3%)	57 (73.1 %)	11 (50.0%)	
TGL (mg/dL)	< 150	25 (40.3%)	30 (38.5%)	12 (54.5%)	0.39
	≥ 150	37 (59.7%)	48 (61.5%)	10 (45.5%)	
FBS (mg/dL)	≤ 100	48 (77.4%)	50 (64.1%)	13 (59.1%)	0.14
	101 - 125	14 (22.6%)	28 (35.9%)	9 (40.9 %)	
HbA1C	≤ 5.6	37 (59.7%)	46 (59.0%)	12 (54.5%)	0.91
	5.7 - 6.4	25 (40.3%)	32 (41.0%)	10 (45.5%)	
S. insulin	≤ 9	51 (82.3%)	60 (76.9%)	10 (45.5%)	0.002
	> 9	11 (17.7%)	18 (23.1%)	12 (54.5%)	
HOMA-IR	< 1.0	15 (24.2%)	22 (28.2%)	1 (4.5%)	< 0.0001
	1 - 1.5	16 (25.8%)	13 (16.7%)	3 (13.6%)	
	1.5 - 2.0	14 (22.6%)	7 (9.0%)	1 (4.5%)	
	2.0 - 2.5	10 (16.1%)	7 (9.0%)	5 (22.7%)	
	≥ 2.5	7 (11.3%)	12 (15.4%)	12 (54.5%)	

BMI: basal metabolic index; WC: waist circumference; HTN: hypertension; T.CHO: total cholesterol; LDL: low density cholesterol; TGL: triglycerides; FBS: fasting blood sugar; HbA1c: glycated hemoglobin; HOMA-IR: homeostatic method assessment insulin resistance; NIHSS: National Institutes of Health Sciences Scale.

consent.

Exclusion criteria

Patients with diabetics, stroke in < 18 years, stroke due to cortical venous sinus thrombosis, head injury, subdural hematoma, cerebral tumors, hemorrhagic stroke, meningitis, and cardiac disorders were excluded from the study.

Methods

A standardized, structured interview was conducted and recorded in the proforma after obtaining permission from the institutional ethical committee of Narayana Medical College

and Hospital. Consent was obtained from all the participants in our study group. 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 with other investigations such as brain CT, MRI, echocardiography, and duplex imaging of extracranial arteries. 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). Severity of stroke was assessed by National Institutes of Health Stroke Scale (NIHSS). Based on NIHSS at admission, we divided the patients 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.

Homeostasis model assessment (HOMA) was used to estimate IR and the levels were studied in relation to the stroke severity. In our study, the normal insulin value for non-diabetic adults was 0.7 - 9 μIU/mL and values > 9 μIU/mL were taken as hyperinsulinemia. IR was defined as HOMA-IR ≥ 2.5. Statistical analysis was done by using IBM SPSS Version 20.0. All the P-values less than 0.05 were considered as statistically significant.

Results

A total of 162 non-diabetic ischemic stroke patients were enrolled according to inclusion and exclusion criteria. The stroke subtypes according to TOAST classification are: 1) atherothrombotic infarction (large-artery atherosclerosis) (n = 97); 2) lacunar infarction (small-artery occlusion) (n = 65); and 3) cardioembolism (n = 0).

Demographic characteristics

Of the patients, 116 (71.6%) were males and 46 (28.4%) were females. Males were outnumbered females with the ratio of 4.8:1. The mean age of the patient was 55.98 years (range 26 - 85 years). Large numbers of male (55) and female (23) patients were presented with NIHSS score of 9 - 18. Twenty-two patients were presented with NIHSS score > 18 (16 males and six females). Most of the patients were fall in between 50 and 59 years age group followed by 40 - 49 years age group (Table 1).

Risk factors

The most common risk factor found was hypertension in 98 (60.5%) patients, followed by smoking in 75 (46.29%) patients and 64 (39.51%) patients were alcoholics. BMI ≥ 23 was observed in 132 (81.48%) patients. Sixty-three (54.3%) males had WC ≥ 90 cm and 31 (67.3%) females had WC ≥ 80 cm. Deranged lipid profiles were observed in most of the patients. Sixty-four (39.5%) patients had total cholesterol ≥ 200 mg/dL, 106 (65.4%) patients had LDL > 100 mg/dL, and 95 (58.64%) patients had triglycerides ≥ 150 mg/dL (Table 1).

IR

Hyperinsulinemia, i.e. serum insulin > 9 μU/mL, was observed in 41 (25.30%) patients. IR with HOMA-IR ≥ 2.5 was noted in 31 (19.13%) patients. Patients with NIHSS score 1 - 8 were 62 (38.27%), NIHSS score 9 - 18 were 78 (48.14%), and NIHSS score > 18 were 22 (13.58%). Stroke patients with high NIHSS score of > 18 (group III) were males (72.7%), in the age group of 50 - 59 years (36.4%), and hypertensives (63.6%). Patients with high NIHSS score of > 18 (group III) had BMI ≥ 23 (77.3%), WC of ≥ 80 cm in females (16.1%), serum insulin > 9 μU/mL (54.5%), and HOMA-IR ≥ 2.5 (54.5%) (Table 1).

Of all the demographic and biochemical variables, NIHSS score in severity (group III) was strongly associated with serum insulin > 9 μU/mL (54.5%) (P = 0.002) and HOMA-IR ≥ 2.5 (54.5%) (P < 0.0001).

Discussion

There have been major efforts to identify modifiable risk factors that could reduce the incidence of ischemic stroke. The role of traditional risk factors like hypertension, DM, dyslipidemia and obesity is well proven in renowned studies. IR is emerging as a novel potentially modifiable risk factor in ischemic stroke patients. IR along with other risk factors predisposes an individual to a greater risk of developing ischemic stroke that if diagnosed and treated early can prevent the major mortality and morbidity associated with stroke. Many studies have established etiological role of IR in ischemic cardiovascular disorders. In present study, we tried to assess the significance of IR as etiology in cerebrovascular disease and its severity.

We report a descriptive study conducted at a single tertiary care hospital and stroke research center. The objective of the study was to estimate the prevalence of IR in non-diabetic ischemic stroke patients and to assess whether it contributes to severity of ischemic stroke. We also analyzed our study for clustering of the traditional risk factors like hypertension, hyperlipidemia, and obesity in non-diabetic ischemic stroke patients with IR.

IR can increase the risk of stroke through non-traditional cardiovascular risk factors, including endothelial dysfunction, increased inflammation, and increased coagulation [8, 9]. IR can be easily assessed by HOMA. According to Misra and Vikram [3], overall the prevalence of IR in Asian Indians (about 5-50%) was reported to be highly variable. According to Rundek et al [10], IR may affect up to 40% of healthy subjects, but data linking this prediabetic state and stroke risk are controversial and limited.

In our study, of 162 non-diabetic ischemic strokes patients, overall we found that metabolic syndrome components were high. That is patients with history of hypertension were 60.5%, high WC and high triglycerides of above normal were seen in 58.02% and 59.25%, respectively and low HDL of below normal was seen in 53.08%. According to Olijhoek et al, prevalence of metabolic syndrome in stroke patients is 43% [11]. Limited information is available; whether or not metabolic syndrome confers a risk greater than the sum of its com-

ponents is controversial. Our findings suggest that metabolic syndrome is associated with stroke but not independent to the sum of its components.

HOMA-IR is the standard method of assessing IR used in stroke patients in various studies with different cutoff values. In Northern Manhattan Study [6], HOMA-IR > 3 was present in 23% of subjects (13% White, 18% Black, and 69% Hispanics), and in study by Park et al [12], HOMA-IR ≥ 1.5 was seen in 33.6%. In our study, significant IR as assessed by HOMA-IR of ≥ 2.5 was prevalent in 19.1% of patients. According to Misra and Vikram [3], these variations in IR could be due to tremendous heterogeneity of Asian Indians in terms of their geographical location and partial adaptation of lifestyle of the country of residence, in addition to variations due to age, gender, and socio-economic strata. Important and consistent observations related to high prevalence of IR in Asian Indians are the presence of excess body fat and abdominal obesity. Variations in IR could also be due to different methodologies employed for the assessment of IR.

Majority of studies on IR and stroke were in the age group of 35 - 68 years in ARIC [4] and Northern Manhattan Study [6]. In our study, it was 26 - 85 years. In our study, males (71.6%) were more compared to females (28.4%), but in Northern Manhattan Study, 63% were females. 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 0.002 and 0.0001, respectively, compared to other traditional risk factors like hypertension and obesity.

The present study demonstrated positive relationship between HOMA-IR and ischemic stroke in non-diabetic patients adjusting for traditional risk factors for stroke, which is similar to the studies done by Rundek [6] in western population and Nakamura et al [13] in Asians and in Bruneck study [14]. This finding suggests that IR has alternative pathways directly related to inflammation, atherosclerosis and stroke and IR is considered an important independent marker of stroke risk. This finding is supported by the fact that South Asians are more insulin-resistant compared with white Europeans and express increased metabolic features of IR. IR significantly clusters with fibrinolytic and coagulation factors in South Asians, which may contribute to high prevalence of vascular disease in this population [15].

In contrast to our study, a large cohort study done in healthy middle-aged Helsinki Policemen Study [16] found hyperinsulinemia and IR were associated with non-diabetic ischemic stroke, but not independent of traditional vascular risk factors and metabolic syndrome. Another similar prospective population-based cohort study among non-diabetic elderly people, done by Renske et al [17] found no association between IR and risk of stroke or the stroke subtypes like cerebral infarction and hemorrhage. Further more multicentered prospective trials can throw more light on this novel risk factor of stroke.

Conclusions

IR may be a novel therapeutic target for stroke prevention. IR can be considered as a risk factor for stroke, because it can be not only measurable but also treatable. High HOMA-IR was associated with high NIHSS score and it is an useful index for prediction of ischemic stroke in non-diabetics. IR with compensatory hyperinsulinemia is likely to have an independent effect on incidence of stroke separately from that of the metabolic syndrome components.

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Conflicts of Interest

The authors have no conflicts of interest to disclose.

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