



ORIGINAL RESEARCH PAPER

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ASSOCIATION BETWEEN INSULIN RESISTANCE AND ISCHEMIC STROKE IN NON DIABETIC ELDERLY PATIENTS

KEY WORDS: Insulin Resistance, Ischemic Stroke, HOMA-IR

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ABSTRACT

The objective of this study was to investigate the association of insulin resistance and ischemic stroke in non diabetic elderly patients. A case-control study on 40 consecutive elderly ischemic stroke (age > 60 years) and 40 controls were recruited from Adam Malik General Hospital, Medan, Indonesia between October 2017 and March 2018. Insulin resistance was defined as Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) \geq 2.5. Data analyzed using chi square with 95% confidence intervals. Levels of HOMA-IR were significantly higher in case than control groups. There was a significant association between insulin resistance and ischemic stroke ($p=0.014$). Insulin resistance in non diabetic elderly patients will increase the risk of ischemic stroke.

Introduction

Stroke is the third leading cause of death after ischemic heart disease and malignancy.¹ In addition, stroke is a major cause of disability in adults, more than half of stroke patients who survive will become dependent and require long-term health care.^{2,3} The prevalence of ischemic stroke increased significantly with age. Age is the most important nonmodifiable risk factor for all stroke types, including ischemic stroke.^{4,5}

Elderly people are more susceptible to insulin resistance than young individuals, and some of them will have type 2 diabetes. Pathophysiology is thought to be due to biological aging, environmental or lifestyle factors. Decreased of muscle mass/ changes in muscle composition, poor dietary habits, and physical inactivity affect insulin resistance in elderly people.⁶

Insulin resistance is a metabolic disorder characterized by decreased tissue sensitivity to insulin caused by environmental factors such as sedentary lifestyle, obesity, and genetics.^{7,8} Insulin resistance is a risk factor for atherosclerosis. Insulin resistance is associated with symptomatic cardiovascular disease (CVD) in the general population. Insulin resistance is an important target for lowering CVD risk.^{9,10}

Insulin resistance is involved in disorders of lipid metabolism, endothelial dysfunction, hypertension, and atherosclerosis, which play a role in CVD abnormalities including ischemic stroke.¹¹⁻¹⁴ Insulin resistance in type 2 diabetes patients increases the risk of all subtypes of ischemic stroke.^{15,16} Previous studies had showed that measures of insulin resistance have been associated with stroke risk in nondiabetic adults,^{13,17} but there was a study reported insulin resistance was unlikely to contribute the risk of subclinical CVD. There was no significant association between insulin resistance and the amount of coronary artery calcium.¹⁸

We used the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) to quantitate insulin resistance and not the gold standard hyperinsulinemic-euglycemic clamp because of practical limitations derived from our clinical setting. However, our selected method has been shown to correlate reasonably well with clamp-derived values.¹⁹ Most studies were based on relatively small numbers of events and included middle-aged but not elderly people, whereas elderly people are at the highest risk of stroke.²⁰ The aim of this study was to investigate the association of insulin resistance and ischemic stroke in non diabetic elderly patients.

Methods

Patient Selection

This study was a case-control study on 40 consecutive elderly ischemic stroke (age \geq 60 years) and 40 controls were recruited from Adam Malik General Hospital, Medan, Indonesia between

October 2017 and March 2018. Ischemic stroke was confirmed by a neurologist and computerized tomography (CT) scan or magnetic resonance imaging (MRI) to exclude other neurological causes. Exclusion criteria were history of diabetes mellitus, use of diabetes medication, or glycated hemoglobin $>6.5\%$. Forty healthy people who were matched by age, sex, body mass index, total cholesterol, and LDL levels were chosen as controls. Written informed consent were obtained from all participants or their caregivers. This study was approved by the Institutional Review Board of Universitas Sumatera Utara.

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 . Insulin resistance was defined as HOMA-IR \geq 2.5.²¹

Diagnosis of insulin resistance

Blood was collected from fasting patients to measure the fasting blood glucose and fasting insulin. Venous blood samples were taken after an overnight fast and stored at -80°C in a number of 5 mL aliquots. Serum glucose levels were determined by using the glucose hexokinase method within 1 week after sampling.²² Serum insulin levels were measured on a Roche Modular Analytics E170 analyzer (Roche Diagnostics GmbH, Germany) by electrochemiluminescence immunoassay technology. The following formula was used to calculate HOMA-IR: [fasting insulin (mU/L) \times fasting glucose (mmol/L)] / 22.5.¹⁹

Statistical analysis

SPSS version 22 (SPSS Inc., Chicago) was used for analysis. The data were analysed using univariate and bivariate analysis with 95% confidence intervals. The results were expressed as the mean \pm standard deviation. Bivariate analysis was carried out using the chi square with a p-value < 0.05 was considered statistically significant.

Results

Case and control groups were homogeneous by age, sex, BMI, total cholesterol, and LDL level ($p>0.05$).

Table 1. Baseline characteristics in case and control groups

Variable	Cases n=40	Controls n=40	p
Age, years, mean \pm SD	67 \pm 4.01	66.2 \pm 3.98	0.769
Gender, n (%)			
Male	24 (52.2%)	22 (47.8%)	
Female	16 (47.1%)	18 (52.9%)	0.651
BMI, kg/m ² , mean \pm SD	24.8 \pm 1.48	24.3 \pm 1.46	0.137

Total cholesterol, mg/dL, mean±SD	209.8 ± 5.39	190.1 ± 4.72	0.359
LDL, mg/dL, mean±SD	142.5 ± 4.65	143.6 ± 3.78	0.885

*p<0.05

There were significant difference in HOMA-IR levels between case and control groups (p<0.001). Levels of HOMA-IR were significantly higher in case than control groups (Table 2 and Figure 1).

Table 2. HOMA-IR levels in case and control groups

	Cases	Controls	p
HOMA-IR	2.61 ± 0.33	2.39 ± 0.32	0.006*

*p<0.05

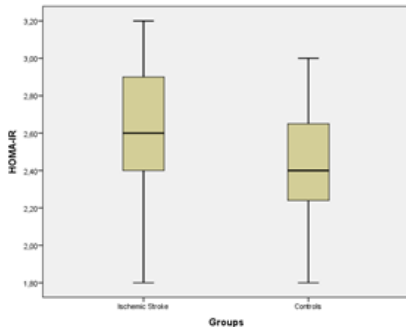


Figure 1. Levels of HOMA-IR in ischemic stroke and control groups

There were significant difference of HOMA-IR levels in severity of stroke (p=0.014). Significantly higher HOMA-IR levels in group III were compared with group I. There were no significant difference in HOMA-IR levels between group II and I and also between group II and III of ischemic stroke patients (Table 3 and Figure 2).

Table 3. HOMA-IR levels in severity of ischemic stroke

	Group I	Group II	Group III	p
HOMA-IR	2.49 ± 0.3	2.52 ± 0.31	2.87 ± 6.37*	0.014*

*p<0.05, #the result of this category was significantly different with group I

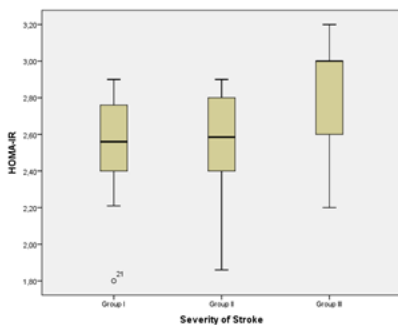


Figure 2. Levels of HOMA-IR in severity of stroke

There was a significant association between insulin resistance and ischemic stroke (p=0.014). Patients with insulin resistance increased the risk of 1.77 times for an ischemic stroke (Table 4).

Table 4. Association between insulin resistance and ischemic stroke in non diabetic elderly patients

Insulin resistance	Group		p	PR (95% CI)
	Ischemic Stroke	Controls		
Yes	26 (63.4%)	15 (36.6%)	0.014*	1.77 (1.09-2.85)
No	14 (35.9%)	25 (64.1%)		

*p<0.05

Discussion

Ischemic stroke is a major cause of disability in elderly people.²³ Stroke is associated with type 2 diabetes, where type 2 diabetes is a major risk factor for vascular disease including ischemic stroke and can lead to worse prognosis in acute ischemic stroke. Previous studies reported that insulin resistance in type 2 diabetes patients increased risk of ischemic stroke.²⁴⁻²⁶ Studies that evaluate the association between insulin resistance and ischemic stroke in non diabetes patients were still limited. Studies that evaluated those association were generally done in the middle aged patients but not elderly people, whereas advanced age increases the risk of experiencing ischemic stroke.²⁷ So this study was conducted to determine the association between insulin resistance and ischemic stroke in non diabetic elderly patients. This study used HOMA-IR as a marker of insulin resistance. HOMA-IR was reported to correlate better with the euglycemic hyperinsulinemic glucose clamp technique than fasting insulin levels, epidemiologic studies tend to use HOMA-IR as a marker for insulin resistance.^{19,28}

There were significant difference in HOMA-IR levels between case and control group. Levels of HOMA-IR were significantly higher in case than control group. In addition, levels of HOMA IR were significantly higher in severe stroke (NIHSS score at admission >18) compared with mild stroke (NIHSS score at admission 1 – 8). These results indicate that insulin resistance, precursor stages of diabetes mellitus, was a risk factors of ischemic stroke in non diabetic elderly patients. This study showed that patients with insulin resistance increased the risk of 1.77 times for an ischemic stroke.

Insulin resistance increases the risk of atherosclerosis and hypercoagulability so insulin resistance is closely related to cardiovascular disease.²⁹⁻³² Cohort study of nondiabetic individual reported that insulin resistance was associated with a 2.8-fold increased risk of first ischemic stroke.¹³ Kumara et al found that high HOMA-IR was associated with high NIHSS score and it was a useful index for prediction of ischemic stroke in non-diabetics.³³ IRIS trial by Kernan et al indicated that oral antidiabetic such as pioglitazone therapy could decrease the risk of vascular events in stroke or transient ischemic attack patients with metabolic syndrome. The results of the IRIS trial showed that patients with insulin resistance should be treated to reduce their risk of a subsequent stroke. Early treatment with pioglitazone could be considered for nondiabetic patients with ischemic stroke or transient ischemic attack in the acute phase.¹⁷

The ACROSS-China registry (Abnormal Glucose Regulation in Patients with Acute Stroke Across China) found that stroke patients who experienced recurrence or mortality within 1 year were more likely to have insulin resistance.³⁴ Hishinuma et al also indicated that insulin resistance may be associated with recurrence of ischemic stroke or ischemic heart disease in patients with stroke.³⁵ Other studies also showed that higher insulin resistance was associated with poor outcome after thrombolytic treatment of ischemic stroke.^{36,37}

Insulin resistance causes prothrombotic and proinflammatory condition, characterized by derangement in endogenous fibrinolysis and increased platelet activation.³⁸ In conditions of insulin resistance there will be an increase in proinflammatory cytokines that induce responses of local inflammatory, enhances platelet adhesion, activation, and aggregation which are associated with ischemic stroke, resulting in exacerbating ischemic damage in the brain. Insulin can have an effect on endothelial cells that may increase cerebral blood flow, so in patients with insulin resistance there may be a decrease in cerebral blood flow.³⁹⁻⁴¹ Insulin resistance can affect clot structure, clot becomes more dense and resistant to lysis. Clots in patients with insulin resistance consist of thick fibers and have longer lysis times than patients without increased insulin resistance.⁴²

Insulin resistance can be considered as a risk factor for stroke. A better understanding of the causes of stroke in the elderly might have important practical implications not only for clinical management, but also for preventive strategies.

The present study has some limitations. Relatively small sample size may limit the generalization of the results. HOMA-IR was measured only at one-time point (at admission). Serial measurements of HOMA-IR were not available.

Conclusion

Insulin resistance in non diabetic elderly patients will increase the risk of ischemic stroke.

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