Ref: Ro J Neurol. 2023;22(2)
DOI: 10.37897/RJN.2023.2.11

HBA1C level and its role on ischemic stroke patients with prediabetes

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ABSTRACT

Background. Stroke is the highest cause of death in Indonesia. Impaired glucose tolerance becomes one of the metabolic risk factors that contribute to ischemic stroke. This study will observe the role of HbA1c level on ischemic stroke in "Dr. Sardjito" General Hospital due to limited research data of this aspect in Indonesia.

Objective. The objective of this study is to explore the role of HbA1c level on ischemic stroke in prediabetic patients of "Dr. Sardjito" General Hospital, Yogyakarta.

Method. This study design is non-experimental, observational study with correlation analysis approach. The research collected 106 data of non-diabetic and prediabetic ischemic stroke patients' medical records in "Dr. Sardjito" General Hospital, recorded from 2012 until 2015.

Result. A Comparison of HbA1c level in prediabetic ischemic stroke patients were significantly higher ($p<0.001$), compared to non-diabetic ischemic stroke patients (mean rank 80.00 vs. 27.00). Multivariate analysis was performed and showed elevated HbA1c level, modified with decreased diastolic blood pressure, associated 70.8% in determining ischemic stroke in prediabetic patients of "Dr. Sardjito" General Hospital.

Conclusion. Elevated HbA1c level, modified with decreased diastolic blood pressure, has significant predisposition role on ischemic stroke patients with prediabetes in "Dr. Sardjito" General Hospital.

Keywords: HbA1c Level, prediabetes, ischemic stroke, Dr. Sardjito General Hospital

List of abbreviations

BKCa – Large Conductance Calcium-activated Potassium channels
BMI – Body Mass Index
CT Scan – Computerized Tomography
DBP – Diastolic Blood Pressure
EDCFs – Endothelium-derived Contracting Factors
HDL-c – High Density Lipoprotein Cholesterol
KATP – Adenosine Triphosphate-sensitive Potassium
LDL-c – Low Density Lipoprotein Cholesterol
MRI – Magnetic Resonance Imaging
RBG – Random Blood Glucose
SBP – Systolic Blood Pressure
TC – Total Cholesterol
TGL-c – Triglycerides Cholesterol

INTRODUCTION

Stroke is the highest cause of death in Indonesia, as much as 328.525 deaths and accounted 23.48% of Indonesia total death in 2014 [1]. Yogyakarta is one of Indonesia province with highest prevalence of stroke. Prevalence of stroke in Daerah Istimewa Yogyakarta reaches 16.9%, which is the second rank of stroke prevalence in Indonesia [2]. Thus, stroke

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Article History:
Received: 25 May 2023
Accepted: 31 May 2023

becomes the leading cause burden of disease in Yogyakarta.

Stroke is an episode of acute neurological dysfunction presumed to be caused by ischemia or hemorrhage, persisting ≥24 hours or until death [3]. Stroke diagnosis can be established by performing non-contrast CT scan, angiography, and MRI. Stroke could be classified into two groups, ischemic stroke and hemorrhagic stroke. Ischemic stroke becomes the most common type of stroke, classified to 87% from all stroke cases in Indonesia. Ischemic stroke is a brain damage that is caused by infarction due to thrombosis blockage of cerebral vascularization. A community-based survey in Indonesia showed a high prevalence of stroke which was associated with increasing age, hypertension, and diabetes mellitus [4]. Multifactorial causes can lead to stroke and Indonesia population has great number for these risk factors.

Diabetes mellitus is one of the risk factors. Yogyakarta is one of the top ten area where has great number of diabetes mellitus cases. It is recorded 12.915 cases of diabetes mellitus in 2013 at Yogyakarta [2]. Diabetes mellitus is a chronic disease caused by inherited and/or acquired deficiency in production of insulin by the pancreas, or by the effectiveness of the insulin produced [5]. It is classified into two types. Type I diabetes mellitus is a chronic metabolic disease which cause hyperglycemia due to autoimmune destruction of β-cell group in pancreas. Type II diabetes mellitus is a chronic metabolic disorder which cause hyperglycemia due to insensitive insulin receptor, relative insulin deficiency, and excessive or inappropriate glucagon expression [6]. Most of the cases accounted 90% in worldwide are developed from impaired glucose tolerance caused by insulin resistance. Impaired glucose tolerance also becomes one of the metabolic risk factors that contribute to ischemic stroke. It is highly related in causing cerebral infarction.

HbA1c is the latest indicator to interpret patient's average glucose profile over 2-3 months. It is categorized as normal if the value below 42 mmol/mol, prediabetes if the value in range 42 to 47 mmol/mol, and diabetes if the value above 48 mmol/mol [6]. Diabetes and prediabetes have significant risk for ischemic stroke [7]. In further study, high HbA1c is associated with higher risk of ischemic stroke in Pakistani population without diabetes [8]. Due to increased risk of diabetes and ischemic stroke in Indonesia, HbA1c could become a valuable predictor of ischemic stroke in prediabetic patient.

There is no further study about role of HbA1c level on risk of ischemic stroke in Indonesia. Therefore, this study will observe the role of HbA1c level on ischemic stroke in "Dr. Sardjito" General Hospital, Yogyakarta.

METHODS

Study design

This study design is non-experimental, cohort retrospective study with correlation analysis approach in order to observe role of HbA1c level on ischemic stroke. All variables were measured in one period. This study collected HbA1c level as independent variable and cerebral infarction as dependent variable. The study observed clinical diagnosis and/or CT scan result to recognize ischemic stroke and observe HbA1c level in medical record.

Subject and population

This research gathered information of ischemic stroke patients from Stroke Unit. Neurology Department of "Dr. Sardjito" General Hospital as population study. Sampling frame for this study was used medical record of the patients, recorded from 2012 until 2015.

Subjects' record that was enrolled in this research fulfilled complete medical record of ischemic stroke patients, contained identity, age from 45 years old above, sex, BMI, smoking status, blood pressure, glucose profile with HbA1c level, and lipid profile. Any subject's record that mentioned status with diabetes mellitus type I, II, and haemotological disorder as exclusion criteria was ruled out from this study.

Data collection was conducted in Stroke Unit of "Dr. Sardjito" General Hospital on October 2018. There were 600 medical records that are observed, recorded from 2012 until 2015. 121 from 600 subjects' data met the inclusion criteria. However, 15 out of 121 included subjects were excluded because the result of CT scan shows hemorrhagic lesion, which are classified as hemorrhagic stroke from data analysis. The final total of analyzed subjects' data is 106.

Study materials and tools

This study used medical record data, which collected from Stroke Unit of "Dr. Sardjito" General Hospital, limited on variables for study purpose. Medical records were taken from neurology department, recorded from 2012 to 2015. Data collection was conducted from September-November 2018.

Statistical analysis

Collected data was processed with SPSS version 16 to interpret the correlation. Normality of the data was analyzed with Kolmogorov-Smirnov test. Comparison of unpaired variables was analyzed with Pearson's Chi Square for categorical variables. For numerical variables, data was analyzed with Mann-

TABLE 1. Bivariate analysis of subjects' characteristics between prediabetic ischemic stroke patients and non-diabetic ischemic stroke patients

Variables		Prediabetic ischemic stroke patients (n=53)	Non-diabetic ischemic stroke patients (n=53)	P-Value	Mean difference (95% CI)	Odds ratio (95% CI)
Age (years)		63.81 (±10,7)	65.47 (±10.9)	0.430[b]	-1.66 (-5.82–2.50)	NA
Sex	Male	32 (60.4%)	35 (66%)	0.546[a]	NA	0.78 (0.36–1.73)
	Female	21 (39.6%)	18 (34%)			
BMI (kg/m^2)		23.31 (±2.9)	23.23 (±2.9)	0.897[b]	0.07 (-1.05–1.19)	NA
SBP (mmHg)		150 (90–210)	160 (100–190)	0.089[c]	NA	NA
DBP (mmHg)		90 (60–122)	97 (60–120)	**0.047**[c]	NA	NA
Smoking Status	Yes	18 (34%)	16 (30.2%)	0.677[a]	NA	1.19 (0.53–2.69)
	No	35 (66%)	37 (69.8%)			
RBG (mg/dl)		111 (67–230)	102 (62–288)	0.343[c]	NA	NA
HbA1c (%)		6.1 (6.0–6.4)	5.5 (4.7–5.9)	**<0.001**[c]	NA	NA
TC (mg/dl)		196.79 (±43.0)	200.06 (±41.7)	0.692[b]	-3.26 (-19.57–13.03)	NA
TGL-c (mg/dl)		108 (54–351)	98 (40–238)	0.140[c]	NA	NA
HDL-c (mg/dl)		44 (13–115)	51 (31–91)	0.207[c]	NA	NA
LDL-c (mg/dl)		131.55 (±39.4)	131.17 (±39.4)	0,961[b]	0.38 (-14.80–15.55)	NA

[a]Chi-square
[b]Unpaired t-test
[c]Mann-Whitney test
Mean rank of Mann-Whitney U test: SBP (case=48.45, control=58.55); DBP (case=47.71, control=59.29); RBG (case=56.33, control=50.67); HbA1c (case=80.00, control=27.00); TGL-c (case=57.91, control=49.09); HDL-c (case=49.74, control=57.26).
Bold indicates significant P-value.
BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; RBG: Random Blood Glucose; TC: Total Cholesterol; TGL-c: Triglycerides Cholesterol; HDL-c: High Density Lipoprotein Cholesterol; LDL-c: Low Density Lipoprotein Cholesterol; NA: Not Applicable

Whitney U test for nonparametric data. The correlation study was analyzed using Eta Correlation Ratio and its significance was measured using Partial Eta Squared Test. The association between HbA1c level, significant confounding factors, and ischemic stroke with prediabetic status was analyzed with Linear Regression test.

RESULTS

Subject characteristics

The case group, prediabetic ischemic stroke patient, is accounted as much as 53 (50%) subjects. The control group, non-diabetic ischemic stroke patient, is accounted as much as 53 (50%) subjects. Observed subjects' characteristics based on determined confounding factors of the research are compared and observed by its distribution on comparison group. Table 1 showed Age, BMI, TC, and LDL-c showed non-significant value in Kolmogorov-Smirnov test, thus these four variables are normally distributed. SBP, DBP, RBG, HbA1c, TGL-c, and HDL-c showed significant value in Kolmogorov-Smirnov test, thus these six variables are not normally distributed (Table 1).

Comparison of baseline characteristics between groups were determined by analyzing distribution and percentage of categorical variables, mean and standard deviation of parametric numerical variables, and median with minimum – maximum value of nonparametric variables. Interpreting from table 1., age, sex, BMI, SBP, smoking status, random blood glucose, total cholesterol, TGL-c, HDL-c, and LDL-c statistically showed non-significant difference between comparison groups ($p>0.05$). SBP, DBP, TGL-c, and HDL-c fulfilled the criteria to be included in multivariate analysis ($p<0.25$). Baseline characteristics between prediabetic and non-diabetic ischemic stroke patients were significantly different in DBP ($p=0.047$) and HbA1c level ($p<0.001$) variables. Based on its mean rank, DBP is significantly higher in non-diabetic ischemic stroke patients and HbA1c level is significantly higher in prediabetic ischemic stroke patients. Therefore, DBP has significant value for non-diabetic ischemic stroke patients and HbA1c level have significant value for ischemic stroke patient with prediabetes. Furthermore, included baseline characteristics in multivariate analysis were analyzed with regression test.

Correlation between HbA1c and prediabetic status of ischemic stroke patients

Correlation ratio between HbA1c level and prediabetic status of ischemic stroke patients was determined with eta correlation test, observed in Table 2.

TABLE 2. Correlation ratio between HbA1c level and prediabetic status of ischemic stroke patients

	Prediabetic status of ischemic stroke patients	
HbA1c	Correlation Ratio (r)	P-Value
	0.837	**<0.001**

Based on Eta Correlation test, matched with linear scatterplot graph, HbA1c level has significant (p<0.001) very strong correlation (r=0.837) with prediabetic status of ischemic stroke patients. Eta correlation test does not define the causal direction of the correlation, thus the direction of fit line to total does not imply the causal direction. To confirm the significance level of eta coefficient, partial eta squared test was conducted to show the power of variant between two variables. Based on Partial Eta Squared test, p-value is below the significance level (p<0.05), thus eta correlation ratio is considered significant. Therefore, there is significant very strong correlation between HbA1c level and ischemic stroke with prediabetic status.

Association between HbA1c level and prediabetic status of ischemic stroke patients

Association between HbA1c level and ischemic stroke with prediabetic status was determined with linear regression test, observed in Table 3. HbA1c level was included as independent variable in this study. SBP, DBP, TGL-c, and HDL-c were included as confounding factors that had significant value (p<0.25) in bivariate analysis.

Based on the result of linear regression test, matched with fulfilled linear regression assumption (linear, normally regressed distribution, no outlier, no collinearity between variables), HbA1c level, modified with DBP, have very strong association with prediabetic ischemic stroke status. HbA1c level contributed as significant (p<0.001) very strong positive correlation (r=0.827) in causing ischemic stroke to prediabetic patients. DBP contributed as significant (p=0.035) very weak inversed correlation (r=-0.113) in causing ischemic stroke to prediabetic patients.

The linear regression model was formulated into Ischemic Stroke with Prediabetes = (-5.058) +(1.027xHbA1c level)-(0.004xDBP). HbA1c level, modified with DBP, contributed 70.8% in determining ischemic stroke with prediabetes. Therefore, elevated HbA1c level, modified with decreased DBP, have 70.8% chances to develop ischemic stroke in prediabetic patients of "Dr. Sardjito" General Hospital.

DISCUSSION

Association between HbA1c level and prediabetic status of ischemic stroke patients

In this cohort retrospective study of 106 ischemic stroke patients in "Dr. Sardjito" General Hospital, the result showed there is significant difference between prediabetic and non-diabetic ischemic stroke patients. The result interpreted HbA1c level is significantly higher in prediabetic ischemic stroke patients (mean rank of case=80.00 vs. control=27.00). It is matched with previous study which showed HbA1c values were significantly higher in diabetic ischemic stroke patients (7.6±2.1 vs. 6.1±2.3) of Pakistani population [8]. In other previous study, adjusted gender,

TABLE 3. Multivariate analysis of HbA1c level on prediabetic status of ischemic stroke patients

Parameter	Result	Description
Model (P-Value)	HbA1c level with diastolic blood pressure P-value: HbA1c Level<0.001 Diastolic Blood Pressure=0.035	Systolic blood pressure, TGL-c, and HDL-c as confounding factors were ruled out from regression model with backward method
Assumption	Linearity: Accepted Normality: Accepted Mean Zero Residue: Accepted Residual Constant: Accepted Independent: Accepted Collinearity: Absence	Scatterplot analysis showed linear graph. Histogram analysis showed normal distribution Mean = 0. Residual graph was not formed certain pattern. Durbin-Watson value close to 2. Tolerance>0.4.
Formula	Ischemic Stroke with Prediabetes= (-5.058)+(1.027xHbA1c level)-(0.004xDiastolic Blood Pressure)	
Adjusted R^2	70.8%	HbA1c level, modified with diastolic blood pressure, contributed 70.8% in determining ischemic stroke with prediabetes.
Correlation Coefficient	HbA1c Level= 0.827 Diastolic Blood Pressure= -0.013	Very strong positive correlation. Very weak inversed correlation.

hypertension, dyslipidemia, and smoking status, HbA1c level had no significant association with all-cause and cardiovascular mortality in Hoorn population [9]. Further analysis was conducted in this study to see the correlation between HbA1c level and ischemic stroke with prediabetic status.

Further analysis between HbA1c level and prediabetic status of ischemic stroke patients was conducted to observed causal effect between HbA1c levels with ischemic stroke with prediabetic status. Eta correlation ratio test showed significant very strong correlation between HbA1c level and ischemic stroke with prediabetic status. The correlation coefficient showed HbA1c level has 0.837 strength to ischemic stroke with pediatric status in "Dr. Sardjito" General Hospital patients. Linear regression test showed HbA1c level contributed as significant ($p<0.001$) very strong positive correlation ($r=0.827$) in causing ischemic stroke to prediabetic patients and DBP contributed as significant ($p=0.035$) very weak inversed correlation ($r=-0.113$) in causing ischemic stroke to prediabetic patients. Elevated HbA1c level, modified with decreased DBP, and contributed 70.8% on determining ischemic stroke in prediabetic patients of "Dr. Sardjito" General Hospital.

Other studies showed raised HbA1c level could be an independent risk factor for stroke in people with and without diabetes, with relative risks similar to those previously reported for coronary heart disease [7]. Higher HbA1c indicated a significantly increased risk for ischemic stroke after adjusting for other confounding variables in Pakistani population without diabetes [8]. Significant difference of HbA1c level between prediabetic and non-diabetic ischemic stroke, significant correlation between HbA1c level and ischemic stroke with prediabetic status, and significant association between HbA1c level, modified with DBP, and ischemic stroke with prediabetes in this study developed assumptions of earlier development of ischemic disturbance in intracranial arteries due to hyperglycemic condition.

This correlation may be proven by other study which showed there is an association exists between higher level of HbA1c and peripheral arterial disease, even among patients without diabetes [10]. Peripheral arterial disease contributes to endothelial dysfunction by activating Large Conductance Calcium-activated Potassium (BKCa) channels and producing Endothelium-derived Contracting Factors (EDCFs). EDCFs worsen impaired vasodilatation and leads to major Adenosine Triphosphate-sensitive Potassium (KATP) disturbance [11]. This disturbance caused influx of sodium to intracellular and causing cytotoxic edema, corresponding into ischemic cascade. These cascades could be proven by other study that showed glucose level in acute stroke patients influence growth of infarct volume, and leads to neurological deterioration among non-diabetic patients with ischemic stroke [12].

Other pathway that could lead HbA1c level to be correlated to ischemic stroke with prediabetic condition was latent hyperglycemic condition that induces systemic inflammation, early arteries stiffness, and microvasculature disturbance in capillary basal membrane [13]. These conditions accelerate the formation of atherosclerosis and its occurrence in intracranial arteries may lead to ischemic stroke. Chronic ischemic cascade and acceleration of atherosclerosis due to latent hyperglycemic state could impact the clinical outcome of ischemic stroke. A prospective study in "Dr. Sardjito" General Hospital showed hyperglycemia contributes as a significant predictor for functional outcome and length of stay in ischemic stroke patients [14].

In corresponds to affected baseline characteristics in this study, and its specified group to prediabetic group, further study is required to adjust the baseline characteristics of study to classify HbA1c level as significant value in predicting ischemic stroke in prediabetic patients at "Dr. Sardjito" General Hospital.

Research Limitation

The author was aware to several limitations in this study. Because of this study was conducted with cohort retrospective study and limitation of stroke unit data registry availability from 2012 to 2015, the baseline characteristics could not be adjusted and its result were statistically limited to DBP significant value between compared groups and clinically limited to overweight with low to moderate risk of non-communicable diseases and hypertension status of both prediabetic and non-diabetic ischemic stroke patients.

CONCLUSION

Elevated HbA1c level, modified with decreased diastolic blood pressure, has significant predisposition role on ischemic stroke patients with prediabetes in "Dr. Sardjito" General Hospital.

Conflicts of interest. The authors affirm no conflict of interest in this study.

Disclosure. The authors report no disclosure.

Acknowledgement

The author would like to express gratitude and appreciation to Andre Stefanus Panggabean, MD throughout process of writing this study.

Financial support: none declared

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