Introduction

Stroke is an acute focal or general neurological dysfunction as a result of underlying cerebrovascular disease. Stroke can be broadly classified into ischemic and hemorrhagic stroke. Ischemic stroke, which contribute around 71% of all strokes, results from infarction of artery in the brain, spinal cord, or retina [1]. Stroke is a second leading cause of death worldwide which account for around 5 million death in 2000 [2]. Stroke is also a major cause of long-term disability. Around 45% post-stroke patient had some degree of disability [3].

Diabetes mellitus is a well-known risk factor for ischemic stroke. Chronic hyperglycemia in diabetes mellitus can promote pro-oxidative and pro-inflammatory cytokines which can cause neuronal toxicity. Hyperglycemia could increase matrix metalloproteinase-9, which can cause nerve damage and cerebral edema. Furthermore, hyperglycemia may be responsible for the pro-coagulant state, which can further compromise the blood supply to the penumbral area in acute ischemic stroke [4]. Uncontrolled hyperglycemia is related to worse functional outcome, higher risk of mortality, and increasing cost of care in stroke cases [5].

One of the most important predictors for functional outcomes in ischemic stroke is infarct volume. Larger infarct had worse overall clinical outcome and higher rate of transformation into intracranial hemorrhage [6]. Several studies reveal that infarct volume is associated with glucose level in ischemic stroke. Watila et al. (2014) demonstrated that patients with blood glucose level >126 mg/dL had larger infarct, more severe clinical manifestation at presentation, and worse clinical outcome. However, this study only assessed blood glucose levels at admission, which may not captured the effect of chronic hyperglycemia on infarct volume and functional outcome [7]. This study aims to investigate the correlation between long-term
glycemic control, assessed with hemoglobin A1C (HbA1C) and infarct volume on acute ischemic stroke in Dr. Moewardi General Hospital, Surakarta, Indonesia.

**Methods**

This was an observational, and quantitative study with cross-sectional design in Dr. Moewardi General Hospital, Surakarta, Indonesia from June to August 2020. A total of 38 participants met the inclusion and exclusion criteria were included in this study. Mean age of participant was 58.37 ± 11.49 years and 55.3% were male. Mean infarct volume was 0.46 ± 0.6cc and mean HbA1C was 6.96 ± 2.69%. We analyzed distribution of numeric data using Shapiro–Wilk test, p > 0.05 indicates normal distribution of data. Characteristics of participant and data distribution test are detailed in Table 1.

| Table 1: Characteristics of participant and data distribution |
|------------------|------------------|------------------|
| Variable          | Mean ± SD         | Median (Min-Max) | n (%)  | p       |
| Demography        |                  |                  |        |         |
| Age (years)       | 58.37 ± 11.49    | 55 (38–82)       |        | 0.172*  |
| Sex               |                  |                  |        |         |
| Male              | 21 (55.3)        |                  |        |         |
| Female            | 17 (44.7)        |                  |        |         |
| Risk Factors      |                  |                  |        |         |
| Hypertension history | 17 (44.7)  |                  |        |         |
| Heart Disease History | 21 (55.3)     |                  |        |         |
| Diabetes Mellitus History | 2 (5.3) |                  |        |         |
| Dyslipidemia History | 9 (23.7) |                  |        |         |
| Smoking History   | 29 (76.3)        |                  |        |         |
| BMI (kg/m²)       | 23.01 ± 2.56     | 23 (18.7–2.76)   |        | 0.256*  |
| Infarct           |                  |                  |        |         |
| Location          |                  |                  |        |         |
| Internal capsule  | 7 (18.4)         |                  |        |         |
| Corona radiata    | 12 (31.6)        |                  |        |         |
| Ganglia basalis   | 2 (5.3)          |                  |        |         |
| Nucleus caudatus  | 6 (15.8)         |                  |        |         |
| Nucleus lentiforms| 1 (2.6)          |                  |        |         |
| Pancreas          | 7 (18.4)         |                  |        |         |
| Thalamus          | 3 (7.9)          |                  |        |         |
| Blood Pressure    |                  |                  |        |         |
| Systole (mmHg)    | 168.13 ± 35.34   | 173 (103–254)    |        | 0.213*  |
| Diastole (mmHg)   | 92.21 ± 15.77    | 92 (63–112)      |        | 0.245*  |
| Lipid Profile     |                  |                  |        |         |
| Cholesterol (mg/dL) | 170.79 ± 50.40  | 173 (20–205)     |        | 0.536*  |
| HDL (mg/dL)       | 35.61 ± 13.35    | 34.5 (9–85)      |        | 0.006   |
| LDL (mg/dL)       | 128.97 ± 49.00   | 130 (25–245)     |        | 0.385*  |
| Triglyceride (mg/dL) | 159.53 ± 94.95  | 148.5 (34–429)   |        | 0.001   |
| Glycemic Profile  |                  |                  |        |         |
| RBS level (mg/dL) | 137.39 ± 91.57   | 102 (68–465)     |        | 0.000   |
| 2HPP glucose level (mg/dL) | 117.76 ± 72.11 | 95 (47–363)      |        | 0.000   |
| HbA1C (%)         | 6.96 ± 2.69      | 5.75 (5–14.8)    |        | 0.000   |

We performed bivariate analysis to determine the correlation between infarct volume and laboratory parameters using non-parametric test. Numeric data were analyzed with Spearman correlation test, while categoric data were analyzed using Eta correlation test. Bivariate analysis shows a strong positive correlation between infarct volume and Hba1C with r = 0.898 (p < 0.001). Several confounding variable had a significant correlation with infarct volume, particularly diabetes mellitus history (r = 0.671; p < 0.001), random blood sugar (RBS) (r = 0.466; p = 0.003), fasting blood sugar (FBS) (r = 0.636; p < 0.001), 2 h postprandial (2HPP) glucose level (r = 0.646; p < 0.001), high density lipoprotein (HDL) (r = −0.354; p = 0.029), and triglyceride (TG) (r = 0.429; p = 0.007). Result of Spearman and Eta correlation test are summarized in Table 2.

We also performed multivariate analysis to find correlation between Hba1C, infarct volume, and other confounding variables. We use multiple linear regression on variable with p < 0.250 on bivariate analysis. Based on multivariate analysis, we discovered constant of

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*Normal distribution, BMI: Body mass index, HbA1C: Hemoglobin A1C.

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Table 2: Result of bivariate analysis

| Variable                  | Infarct volume | Regression Coefficient (β) | 95% CI | p-value |
|---------------------------|----------------|----------------------------|--------|---------|
| HbA1C                     | 0.898          |                            | <0.001*|         |
| Other Variable            |                |                            |        |         |
| Age                       | 0.202          | 0.225                      |        |         |
| Sex                       | 0.119          | 0.475                      |        |         |
| Systolic                  | −0.044         | 0.795                      |        |         |
| Diastolic                 | −0.136         | 0.328                      |        |         |
| BMI                       | 0.127          | 0.445                      |        |         |
| Diabetes mellitus history | 0.671          | <0.001*                    |        |         |
| Hypertension history      | 0.025          | 0.880                      |        |         |
| Heart disease history     | 0.143          | 0.391                      |        |         |
| Dyslipidemia history      | 0.261          | 0.113                      |        |         |
| Smoking                   | 0.033          | 0.845                      |        |         |
| RBS level                 | 0.466          | 0.003*                     |        |         |
| FBS level                 | 0.636          | <0.001*                    |        |         |
| 2HPP glucose level        | 0.646          | <0.001*                    |        |         |
| Total cholesterol         | −0.119         | 0.475                      |        |         |
| LDL                       | 0.054          | 0.747                      |        |         |
| HDL                       | 0.429          | 0.001*                     |        |         |
| Triglyceride              |                |                            |        |         |

Discussion

The most participants of this study (55.3%) were male, consistent with epidemiological studies which showed higher prevalence of stroke in male. Wang et al. (2019) found that incidences of stroke were 1652.51 and 920.80/100000 per year in men and women, respectively [9]. Mean age of our participant was 58.37 ± 11.49, similar to study by Misbach and Wendra (2011), which shows mean age of 58.8 ± 13.3 years in stroke patient [10]. In this study, there is no correlation between age and infarct volume. However, studies show that age is an important independent risk factor, where stroke rates doubling every decade after age of 55. Furthermore, age is a significant predictor of stroke clinical outcome, regardless of stroke severity, etiology, thrombolysis efficacy, gender, and other vascular risk factors. Older patients tend to have higher mortality rates and worse functional outcomes [11].

In this study, we calculate infarct volume from head CT-scan sliding with formula of A × B × C/2. CT-scan is rapid and inexpensive imaging modality which makes it ideal for emergency cases and becomes gold standard imaging to diagnose stroke. In contrast to CT-scan, magnetic resonance imaging (MRI) produces images with better resolution, thus make it more sensitive than CT-scan to diagnosed ischemic stroke. However, MRI is relatively expensive and requires longer examination time [12]. In Indonesia, CT-scan, unlike MRI, is done to all patient suspected with stroke, make it as an abundant resource for radiological studies. Routine and A × B × C/2 is a simple, rapid, and reproducible method to measure [13]. However, a study discovered that this formula may overestimated infarct volume in acute stroke. Calculation of infarct volume by Od-value formula of 1.1 (A × B) + 0.03 (A × B)² has higher specificity compared to A × B × C/2 formula [14].

Twenty-nine patients (76.3%) had no previous history of diabetes mellitus, the average value of HbA1C in this study was 6.96 ± 2.69, and 26.3% of patients had HbA1C >6.5%. The American Diabetes Association recommends HbA1C cut-off value of 6.5% to diagnose diabetes. Based on epidemiological studies, HbA1C >6.5% is more prone to vascular complications [5]. In this study, we discovered a statistically significant positive correlation between HbA1C and infarct volume (p < 0.001). Correlation coefficient of r = 0.898 indicates a very strong positive correlation between two variables. Similar result observed in study by Mostafa and Mohamed (2015) which examined the correlation between HbA1C and severity of ischemic stroke. They showed a significant moderate positive relationship (r = 0.489) between HbA1C and infarct size. A strong relationship between pre-stroke glycemic control and functional outcomes was also observed in this study. A poor HbA1C before cerebrovascular accident is adversely correlated with Barthel index score with r = −0.350. It indicates that HbA1C is a reliable independent predictor of stroke severity and functional outcome [15]. Another study also showed that HbA1C had a positive correlation with infarction volume assessed by diffusion weighted imaging MRI in the internal carotid artery region. Sun et al. (2016) found that infarct volume was larger in patients with HbA1c ≥6.36% (mean volume of 16.38 ± 10.48cc) compared...
to patients with HbA1c <6.36% (mean volume of 5.24 ± 5.15cc) [16]. Another study by Lee et al. (2020) also supports this finding. Poor glycemic control, represented by glycated albumin, also correlated with more severe stroke and larger infarct volume. This study found that patient with higher level of glycated albumin had a median infarct volume of around 1.77cm³, compared to median of 0.46 cm³ on patients with lower glycated albumin. Furthermore, higher National Institute Health Stroke Scale score is found on 15.7% of patient with higher value of glycated albumin, compare to only 3.8% of patient with lower glycated albumin [17]. Those finding shows that glycemic control, either assessed with HbA1C or glycated albumin, is correlated with infarct volume and clinical outcome.

Chronic hyperglycemia promotes oxidative stress and mitochondrial superoxide overproduction. Furthermore, it can also leads to the formation of glycation end products of various proteins, which contribute to plaque and atherosclerosis formation [18]. Poor long-term glycemic control also altered the structure and function of the vascular bed in both small and large cerebral blood vessels, as well as acidic and inflammatory state. These conditions could reduce blood supply to the penumbra area in acute ischemic stroke, thereby increasing area of infarction [4], [5].

We observed a significant relationship between RBS, FBS, and 2HPP glucose level with infarct volume on bivariate analysis. Watila et al. (2014) also observed that elevated RBS related to larger infarct. Acute ischemic stroke has reciprocal relation with hyperglycemia. Not only acute ischemic stroke could be worsened by hyperglycemia, it also can induce hyperglycemia. This condition, known as stress hyperglycemia, is caused by increased cortisol level [7]. Another study also highlights that FBP also shows significant relationship with functional outcomes in stroke patients. Lower FBG level is associated with better functional outcome in stroke patient [19]. We also observed a significant correlation between diabetes mellitus history and infarct volume. Our finding is in line with study done by Hjalmarsson et al. (2015), which stated that hyperglycemia as a marker for worse clinical outcome was observed on ischemic stroke with no diabetes mellitus history, but not with patient diagnosed with diabetes mellitus [5].

A systematic-review and meta-analysis on 23 studies evaluating correlation of hyperglycemia and infarct volume show conflicting result. Several studies show that hyperglycemia exacerbates infarct volume. However, greater increased of infarct volume was observed in studies using streptozotocin as diabetogenic agent compared to studies using dextrose infusion, which is more similar to real life pathophysiology of Type 2 diabetes mellitus [20].

We also found that HDL and TGs, but not cholesterol and low density lipoprotein (LDL), had a significant correlation with infarct volume. The study by Pikija et al. (2006) shows that higher serum TG is associated with lower infarct volume in brain CT-scan. Higher TG level also correlated with less severe stroke symptom on onset and lower mortality rate. However, further study is needed to understand the mechanism underlying this effect [21]. History of hyperlipidemia also reduces white matter hyperintensity, which could predict infarct progression and correlate with poor outcome of ischemic stroke [22]. Furthermore, high TG-glucose index, which is calculated with formula of log scale of (fasting TG × fasting glucose)/2, is associated with sooner recurrent ischemic stroke [23]. Hyperlipidemia is also a well-known risk factor for stroke. Hyperlipidemia has been shown to exacerbate ischemic damage through endothelial cell injury, oxidative stress, inflammation, and neuronal loss [24].

Consistent with study conducted by Bonardo et al. (2018), we found that both systolic and diastolic blood pressure did not correlate with infarct volume on ischemic stroke [25]. However, Cipolla et al. (2018) showed that a larger infarct was found in patients with hypertension. Chronic hypertension will result in increasing cerebrovascular resistance, causing cerebral hypoperfusion. Increased vascular tone and narrowed vessels occur could also be found due to chronic hypertension. Cipolla et al. hypothesized that hypertension create poor collateral flow, resulting in fewer tissue that could be revascularized [26].

On multivariate analysis, we observed HbA1C regression correlation of 0.222, which indicates that 22.2% infarct volume are determined by HbA1c. Other major determinant of infarct volume is location of blood vessel blockage in ischemic stroke. Infarction in blood vessel supplies large area in the brain will result in bigger infarct area. Infarction in large blood vessel also result in worse clinical outcome [27]. We did not find any confounding factors that affect infarct volume in ischemic stroke. This result may be caused by strong correlation between confounding factors, we analyzed with HbA1C as independent variable. HbA1C tends to have positive correlation with RBS, FBS, and 2HPP, since they all measure blood glucose level. HbA1C also has a strong correlation with total cholesterol, LDL, and LDL/HDL ratio. The latest study even evaluated HbA1C as a potential biomarker of dyslipidemia. Using HbA1C in Type 2 diabetic patient provides both early diagnostic assessment for dyslipidemia and glycemic control status with relatively inexpensive test [28].

To the best of our knowledge, this is the first study to analyzed correlation between glycemic control and infarct volume in Indonesian population. Our finding emphasizes the importance of blood glucose monitoring in routine clinical examinations to prevent large infarct volume and severe clinical outcome in stroke, particularly in patient with diabetes mellitus. This study also done multivariate analysis to understand correlation between HbA1C and infarct volume, and other confounding factors. Our study is a cross-sectional study which only evaluate correlation...
between two variables. The study with serial HbA1C could provide causality information between glycemic control and infarct volume. More accurate imaging with MRI and analysis with Od-value are needed for better infarct volume estimation, as well as to assess the penumbra area in ischemic stroke. Larger number of participants is required to provide better data that can represent the population.

Conclusions

There is a strong positive correlation between infarct volume and HbA1C, and HbA1C is variable contribute to the volume of infarct.

References

1. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: A statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44(7):2064-89. https://doi.org/10.1161/STR.0b013e318296aeaca PMId:23652265

2. World Health Organization. The Top 10 Cause of Death. WHO; 2020. Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. [Last accessed on 2021 Oct 13].

3. Yang Y, Shi YZ, Zhang N, Wang S, Ungvari GS, Ng CH, et al. The disability rate of 5-year post-stroke and its correlation factors: A National Survey in China. PLoS One. 2016;11(11):1-9. https://doi.org/10.1371/journal.pone.0165341 PMId:27824877

4. Garg R, Chaudhuri UA, Menshauer F, Dandona P. Hyperglycemia, insulin, and acute ischemic stroke: A mechanistic justification for a trial of insulin infusion therapy. Stroke. 2006;37(1):267-73. https://doi.org/10.1161/01.STR.0000195175.29487.30 PMId:16306459

5. Hjalmarsson C, Manhem K, Bokemark L, Andersson B. The role of prestroke glycomic control on severity and outcome of acute ischemic stroke. Stroke Treat. 2014;2014:694569. https:// doi.org/10.1155/2014/694569 PMId:25295219

6. Payabvash S, Taleb S, Benson JC, McKinney AM. Acute ischemic stroke infarct topology: Association with lesion volume and severity of symptoms at admission and discharge. AJNR Am J Neuroradiol. 2017;38(1):58-63. https://doi.org/10.3174/ ajnr.A4970 PMId:27758775

7. Watila MM, Nyandaiti YW, Ahidjo A, Balarabe SA, Ibrahim A, Bakki B, et al. Effect of admission hyperglycaemia on infarct size and clinical outcome in black patients with acute ischaemic stroke, northeast Nigeria. Br J Med Med Res. 2014;4(34):5324-34.

8. Van Der Worp HB, Claus SP, Bär PR, Ramos LM, Algra A, van Ginj J, et al. Reproducibility of measurements of cerebral infarct volume on CT scans. Stroke. 2001;32(2):424-30. https://doi.org/10.1161/01.STR.32.2.424 PMId:11157177

9. Wang Y, Dai Y, Zheng J, Xie Y, Guo R, Guo X, et al. Sex difference in the incidence of stroke and its corresponding influence factors: Results from a follow-up 8.4 years of rural China hypertensive prospective cohort study. Lipids Health Dis. 2019;18(1):72. https://doi.org/10.1186/s12944-019-1010-y PMId:30909919

10. Misbach J, Wendra A. Clinical pattern of hospitalized strokes in 28 hospitals in Indonesia. Med J Indones. 2000;9(1):29-34.

11. Gibson CL. Cerebral ischemic stroke: Is gender important? J Cereb Blood Flow Metab. 2013;33(9):1355-61. https://doi. org/10.1038/jcbfm.2013.102 PMId:23756694

12. Vymazal J, Rilshe AM, Keller J, Janouskova L. The role of prestroke glycemic control on severity and outcome of acute ischemic stroke patients with or without diabetes. J Clin Neurosci. 2015;22(3):498-503. https://doi.org/10.1016/j.jocn.2014.08.030 PMId:25595961

13. Lei C, Wu B, Liu M, Chen Y. Association between hemoglobin A1C levels and clinical outcome in ischemic stroke patients with or without diabetes. J Clin Neurosci. 2015;22(3):498-503. https://doi.org/10.1016/j.jocn.2014.08.030 PMId:25595961

14. Kufner A, Stief J, Siegertin B, Nolte C, Fiebach JB, et al. Two simple and rapid methods based on maximum diameter accurately estimate large lesion volumes in acute stroke. Brain Behav. 2020;10(11):e01828. https://doi.org/10.1002/brb3.1828 PMId:23909402

15. Mostafa MA, Mohamed NA. Effect of glycemic control on the severity and outcome of stroke in Saudi Arabia. Egypt J Neurol Psychiatry Neurosurg. 2015;52(4):228-31.

16. Sun B, Zhao H, Liu X, Lu Q, Zhao X, Pu J, et al. Elevated hemoglobin A1C is Associated with Carotid Plaque Vulnerability: Novel Findings from Magnetic Resonance Imaging Study in Hypertensive Stroke Patients. Sci Rep. 2016;6:33246. https://doi.org/10.1038/srep33246. PMId:27629481

17. Lee SH, Jang MU, Kim Y, et al. Effect of Prestroke Glycemic Variability Estimated Glycated Albumin on Stroke Severity and Infarct Volume in Diabetic Patients Presenting With Acute Ischemic Stroke. Front Endocrinol (Lausanne). 2020;11:230. https://doi.org/10.3389/fendo.2020.00230 PMId:32373074

18. Lei C, Wu B, Liu M, Chen Y. Association between hemoglobin A1C levels and clinical outcome in ischemic stroke patients with or without diabetes. J Clin Neurosci. 2015;22(3):498-503. https://doi.org/10.1016/j.jocn.2014.08.030 PMId:25595961

19. Xue WY, Xu YC, Wu YW, Yang M. Observation of elevated fasting blood glucose and functional outcome after ischemic stroke in patients with and without diabetes. Oncotarget. 2017;8(40):67980-9. https://doi.org/10.18632/oncotarget.19074 PMId:28978089

20. MacDougall NJ, Muir KW. Hyperglycaemia and infarct size in animal models of middle cerebral artery occlusion: Systematic review and meta-analysis. J Cereb Blood Flow Metab. 2011;31(3):807-18. https://doi.org/10.1038/jcbfm.2010.210 PMId:21157471

21. Pijkja S, Milevčić D, Trkulja V, Kidemert-Fiskac S, Pavliček I, Sokol N, et al. Higher serum triglyceride level in patients with acute ischemic stroke is associated with lower infarct volume on CT brain scans. Eur Neurol. 2006;55(2):89-92. https://doi.org/10.1159/000092780
22. Jimenez-Conde J, Biffi A, Rahman R, Kanakis A, Butler C, Sonni S, et al. Hyperlipidemia and reduced white matter hyperintensity volume in patients with ischemic stroke. Stroke. 2010;41(3):437-42. https://doi.org/10.1161/STROKEAHA.109.563502
PMid:2013919

23. Nam KW, Kwon HM, Lee YS. High triglyceride-glucose index is associated with early recurrent ischemic lesion in acute ischemic stroke. Sci Rep. 2021;11(1):15335. https://doi.org/10.1038/s41598-021-94631-5
PMid:34321520

24. Menet R, Bernard M, ElAli A. Hyperlipidemia in stroke pathobiology and therapy: Insights and perspectives. Front Physiol. 2018;9:488. https://doi.org/10.3389/fphys.2018.00488
PMid:29867540

25. Bonardo P, Pantiu F, Chertcoff A, León Cejas L, Pacha S, Uribe Roca C, et al. Blood pressure evolution in young patients with acute ischemic stroke: A new model for understanding the natural course of spontaneous hypertension? Int J Neurosci. 2018;128(2):140-5. https://doi.org/10.1080/00207454.2017.1378198
PMid:28889789

26. Cipolla MJ, Liebeskind DS, Chan SL. The importance of comorbidities in ischemic stroke: Impact of hypertension on the cerebral circulation. J Cereb Blood Flow Metab. 2018;38(12):2129-49. https://doi.org/10.1177/0271678X18800589
PMid:30198826

27. Cheng B, Forkert ND, Zavaglia M, Hilgetag CC, Golsari A, Siemensen S, et al. Influence of stroke infarct location on functional outcome measured by the modified rankin scale. Stroke. 2014;45(6):1695-702. https://doi.org/10.1161/STROKEAHA.114.005152
PMid:24781084

28. Hammed IK, Baydaa Abed FA, FRashid N. Glycated haemoglobin as a dual biomarker association between HbA1c and dyslipidemia in type 2 diabetic patients. J Fac Med Baghdad. 2012;88(1):88-92.