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Association between Increased Matrix Metalloproteinase-9 (MMP-9) Levels with Hyperglycaemia Incidence in Acute Ischemic Stroke Patients

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Abstract

BACKGROUND: Hyperglycemia is common in acute stroke patients. Hyperglycemia can induce the production of reactive oxygen species, causing increased activity of matrix metalloproteinase-9 (MMP-9).

AIM: This study aimed to determine an association between the increased levels of MMP-9 and the incidence of hyperglycemia in acute ischemic stroke patients.

METHODS: This is a case-control study. Acute ischemic stroke patients admitted to the Stroke Unit of a reference hospital in Yogyakarta, Indonesia was divided into the hyperglycemic and non-hyperglycemic group. Demographic and clinical characteristics of each subject were recorded, and blood levels of MMP-9 were measured. Seventy-one patients were recruited, 40 subjects in the hyperglycemic group and 31 subjects in the non-hyperglycemic group.

RESULTS: The median levels of blood MMP-9 level in the hyperglycemic and non-hyperglycemic group were 974.37 and 748.48 ng/mL, respectively, and the difference was statistically not significant (95% CI, 191.24-2849.53; p = 0.07). When the calculated cut-off point of 600.99 ng/mL was used, the proportion of patients with higher MMP-9 levels was significantly more in the hyperglycemic group compared with the ones in the non-hyperglycemic group (82.5% and 54.8%, respectively; OR = 3.88; p = 0.011).

CONCLUSION: We concluded that the proportion of patients with MMP-9 level >600.99 ng/mL was significantly higher in acute ischemic stroke patients with hyperglycemia.

Introduction

Hyperglycemia, as defined by fasting blood glucose over 126 mg/dL (7.0 mmol/L) is common in acute ischemic stroke patients with the incidence rate of approximately 60% [1] [2]. Hyperglycemia in patients with acute stroke can be caused by some of the underlying mechanisms; one of which is the activation of the hypothalamic-pituitary-adrenal axis due to a direct impact of the brain ischemia [3]. This hyperglycemia condition is associated with cytotoxic injury of the brain and increased mortality and poor recovery for the patients [4].

The hyperglycemia may induce the production of reactive oxygen species (ROS), which resulted in the increased activity of matrix metalloproteinase-9 (MMP-9) [5]. Glucose intake is also known to increase levels of pro-inflammatory transcription factors, such as activator protein-1 (AP-1) and the early growth response-1 (Egr-1). AP-1 regulates the transcription of

MMP. Hence the expression of MMP-2 and MMP-9 are increased and rapidly regulated in stroke pathogenesis [6] [7]. It positively correlates with the severity of the stroke, and it increases the permeability of the blood-brain barrier [8] [9] [10]. Polymorphism in MMP-9 (e.g. MMP9 rs3918242) may induce the development of ischemic stroke and is found more frequent in diabetic type 2 patients, indicating the role of the MMP protein in pathological mechanism of stroke [11] [12].

There is evidence that shows the detrimental role of MMP-9, i.e., enlarging the region of brain injury following the focal ischemia. A recent study demonstrated that MMP-9 can directly trigger anoikis, e.g., the death of neurons due to the occurrence of signal interference between cells and their matrix [13]. Inhibition of MMP-9 either by minocycline or gene silencing in ischemic models shows a protective effect as indicated by decreased infarct size, indicating the involvement of MMP-9 in ischemic stroke pathology [14].

The purpose of this study was to determine the relationship between levels of MMP-9 with the incidence of hyperglycemia in patients with acute ischemic stroke.

Material and Methods

This was a case-control study approved by the Ethical Committee of the Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta, Indonesia. Blood samples were consecutively withdrawn from acute ischemic stroke patients who were treated during the first attack at the Stroke Unit in Dr Sardjito General Hospital, Yogyakarta, Indonesia. The inclusion criteria were age 50-70 years, and the maximum onset of stroke was 6 days evidenced by the presence of cerebral infarction in the head CT scan. Subjects were divided into 2 groups, i.e., the hyperglycemic group (fasting plasma blood glucose levels > 126 mg/dL) including patients with a history of diabetes mellitus before the stroke and the non-hyperglycemic group (fasting plasma blood glucose < 126 mg/dL). This study selected subjects with age over 50 years old because a previous study demonstrated that the relationship between MMP-9 with certain complications was also influenced by the age factor. Indeed, it was reported that MMP-9 genotypes were associated with extensive lesions of cardiac infarction in patients aged 53 years and over [15]. The exclusion criteria were patients with bleeding transformation or space-occupying lesion by other causes and patients who did not complete the study procedure.

The analyses of multiple comorbidities on stroke were performed on the recruited subjects, including their demographics, risk factors, blood pressure, blood chemistry, and clinical outcomes based on the Gadjah Mada Stroke Scale (GMSS). GMSS is a modified version of the National Institute of Health Stroke Scale (NIHSS). GMSS is designed to serve as a clinical measurement tool to evaluate and to monitor the neurologic status of stroke patients. The GMSS has been tested for its validity and reliability, in which it yields a Kappa coefficient between 0.85-1. The GMSS threshold is set at 23: score more than 23 indicates mild to moderate neurologic deficits, while the one less than 23 refers to severe neurologic deficits [16]. Plasma blood glucose levels were examined within the first 24 hours of care after fasting for at least 12 hours. The MMP-9 level was measured with the technique of quantitative sandwich enzyme-linked immunosorbent assay (ELISA) using a special kit (Bio-Rad Laboratories, Inc., Hercules, CA 94547, USA). A comparative analysis of MMP-9 levels was conducted between acute ischemic stroke subjects in the hyperglycemic and the non-hyperglycemic groups. To determine the cut-off point of MMP-9 levels, the receiver operating characteristic (ROC) curve was created. Sensitivity and specificity are two components used to measure the validity of a diagnostic test compared to the gold standard. ROC curve is a graph of the sensitivity (Y-axis) with 1-specificity (X-axis), aims to determine the cutoff point of the diagnostic test that is continuous or ordinal scale, and the ROC is an effective method for assessing the performance of a diagnostic test [17]. Spearman correlation analysis was used to analyse the correlation between MMP-9 level and stroke outcome. The Chi-square, t-test or Mann-Whitney analyses were performed for basic demographic characteristics with a chosen significance level of 0.05 or 95% confidence level ($p < 0.05$) by using the statistical program.

Results

Seventy-one patients with acute ischemic stroke were recruited, consisting of 40 hyperglycemic and 31 non-hyperglycemic subjects. The baseline characteristics between the two groups are shown in Table 1. The mean age of both groups was 60 and 58 years, in which the majority of subjects were males with a history of hypertension. As expected, the incidence of diabetes mellitus was higher in the group of hyperglycemia (32.5% vs 6.5%; $p = 0.011$). The systolic blood pressure was higher in hyperglycemia group compared to non-hyperglycemia group (155.90 ± 25.72 mmHg vs 143.13 ± 22.12 mmHg respectively;

p = 0.031). Other variables did not show a significant difference between the two groups.

Table 1: Baseline characteristics of the subjects

Variables	Hyperglycemia (n = 40)	Non-hyperglycemia (n=31)	Total	t/χ^2	p
Demography					
Age (years)	60.55 ± 8.64	57.90 ± 12.56	59.39 ± 10.53	1.051	0.297
Male (n; %)	22 (55.0%)	19 (61.3%)	41 (57.7%)	0.283	0.595
Female (n; %)	18 (45.0%)	12 (38.7%)	30 (42.3%)		
Therapeutic windows (hour)	28.13 ± 26.23	25.32 ± 27.02	26.90 ± 26.42	0.441	0.661
Risk Factor of stroke					
Hypertension (n; %)	29 (72.5%)	18 (58.1%)	47 (66.2%)	5.697	0.058
Diabetes Mellitus (n; %)	13 (32.5%)	2 (6.5%)	15 (21.1%)	8.970	0.011
Cardiac disease (n; %)	3 (7.5%)	3 (9.7%)	6 (8.5%)	0.367	0.832
Hypercholesterolemia (n; %)	9 (22.5%)	4 (12.9%)	13 (18.3%)	1.101	0.577
Smoking cigarette (n; %)	15(37.5%)	8 (25.8%)	23 (32.4%)	1.090	0.296
Blood pressure					
Systolic (mmHg)	155.90 ± 25.72	143.13 ± 22.12	150.32 ± 24.88	2.204	0.031
Diastolic (mmHg)	89.00 ± 13.05	85.52 ± 12.58	87.48 ± 12.87	1.133	0.261
Blood chemistry					
BUN (mg/dL)	18.77 ± 12.72	17.27 ± 11.15	18.11 ± 12.00	0.520	0.605
Creatinine (mg/dL)	1.07 ± 0.56	1.21 ± 1.35	1.13 ± 0.98	-0.592	0.556
Total cholesterol (mmol/L)	204.78 ± 52.01	188.19 ± 44.86	197.54 ± 49.38	1.413	0.162
LDL (mmol/L)	130.56 ± 47.34	117.45 ± 39.55	124.84 ± 44.29	1.242	0.218
Albumin (g/dL)	3.10 ± 0.63	3.20 ± 0.60	3.14 ± 0.62	-0.613	0.542
Stroke outcome					
Gadjah Mada Stroke Scale (GMSS)	25.25 ± 8.93	28.52 ± 8.14	26.68 ± 8.69	-1.588	0.117

BUN: blood urea nitrogen, LDL: low-density lipoprotein.

Figure 1 illustrates the distribution of MMP-9 levels between the two groups. The median levels of MMP-9 in the hyperglycemic group were higher than the ones in the non-hyperglycemic group (974.37 and 748.48 pg/mL, respectively). No outlier data were observed.

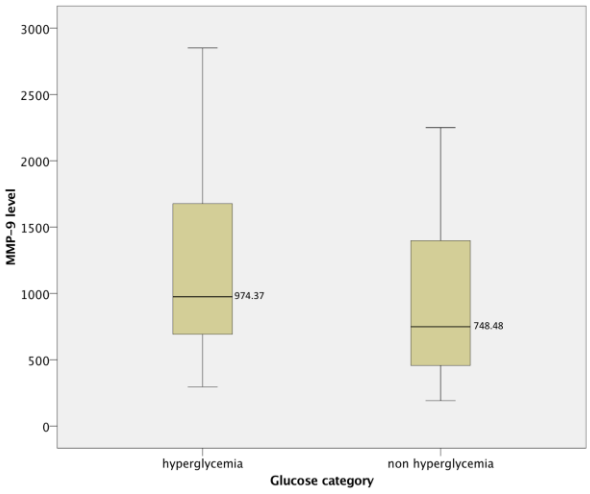

Figure 1: Boxplot distribution of MMP-9 levels in the hyperglycemic and non-hyperglycemic groups. The bottom and top of the box showed the first and third quartiles, while whisker shows the range between + 1.5 Inter Quartile Range (IQR) and the first quartile -1.5 IQR. The median was shown as a horizontal line in the box as well as a number beside the box

Subsequent analysis with the Mann-Whitney test indicated that the hyperglycemic group had a higher sum of the rank of MMP-9 levels than the ones in the non-hyperglycemic group (1596.5 and 959.5 ng/mL, respectively), although the difference was statistically not significant (95% CI, 191.24-2849.53; p = 0.07).

Next, by using the ROC curve, the cut-off point for MMP-9 was obtained, i.e., 600.99 ng/mL (Figure 2). Table 2 shows the association of the MMP-9 levels based on the cut-off point. The proportion of MMP-9 levels > 600.99 ng/mL in hyperglycemia group was 82.5%, higher than the ones in the non-hyperglycemia group (54.8%). This was significantly different based on the value of risk estimated by the calculated odds ratio (OR) = 3.88 (95% CI, 1.319-11.428; p = 0.011).

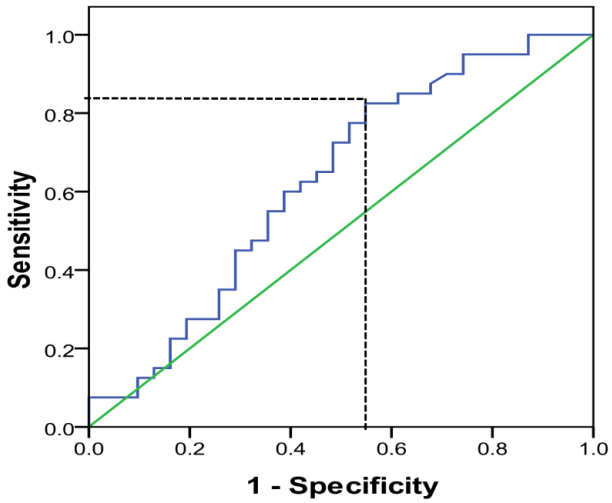

Figure 2: Receiver Operating Characteristic (ROC) curve to determine the cutoff point of the MMP-9 levels

Previous studies have shown adverse effects of MMP-9 levels on stroke outcomes [8]. However, no significant association between the MMP-9 levels with the stroke outcomes (as assessed with GMSS) was observed in this study (p = 0.214).

Table 2: Bivariate analysis of MMP-9 to the Hyperglycemic and Non-hyperglycemic Group

MMP-9 (ng/mL)	Hyperglycemia		Non-hyperglycemia		χ^2	p	OR	95%CI	
	n	%	n	%				Lower limit	Upper limit
≥600.99	33	82.5	17	54.8	6.416	0.011	3.88	1.319	11.428
<600.99	7	17.5	14	45.2					

The patients subsequently were divided into two groups based on the MMP-9 levels, i.e., one group above the cut-off point (≥ 600.99 ng/mL) and another one below the cut-off point. However, no significant difference between the two groups regarding clinical outcomes according to the GMSS was observed based on the Mann-Whitney analysis (p = 0.91).

Discussion

In our study, the MMP-9 levels ≥ 600.99 ng/mL were observed more frequently in the hyperglycemic group than in the non-hyperglycemic group. These results support previous studies which demonstrated that the incidence of hyperglycemia is associated with elevated MMP-9 levels [17].

Hyperglycemia is a common phenomenon among acute stroke patients, with the incidence rate of approximately 60% [2]. An increased blood glucose level is associated with various complications affecting the central nervous system. Hyperglycemia during an ischemic stroke has been associated with an increased risk of mortality and poor functional outcome [17] [18]. This can be due to the up-regulation of many neurotoxic mediators (e.g., MMP-9) released by cells that are stimulated by high blood glucose levels. Previous studies have shown that hyperglycemia will increase the incidence of oxidative stress and the activation of MMP-9, which subsequently exacerbating the dysfunction of the blood-brain barrier after ischemic injury / re-perfusion and cerebral oedema [19]. However, it is elusive yet of how high of blood glucose level to trigger an elevation in MMP-9 level and of how high the MMP-9 level could rise as a result of hyperglycemia [10] [21].

We proposed in this study that the cut-off point of the MMP-9 level was 600.99 ng/mL. MMP-9 levels above the cut-off point were more frequently encountered in the hyperglycemic group than in the non-hyperglycemic group. These results have some significant impacts. First, our study reconfirms findings from previous studies showing that hyperglycemia is associated with increased levels of MMP-9 [17]. This elevation of MMP-9 in hyperglycemia was also found in another condition such as severe sepsis, indicating that the process does not depend on the diabetic status of the patient before a stroke [22]. Second, this study showed a cut-off point for the elevation of MMP-9 levels due to hyperglycemia. This implies in clinical practice. Clinicians should be aware that when a hyperglycemic patient has an MMP-9 level above the cut-off point, oxidative stress has already occurred. This, in turn, will affect the outcome of stroke and other complications that may arise. In summary, we hypothesise that MMP-9 level ≥ 600.99 ng/mL can be a predictor for poor outcomes of ischemic stroke.

Several studies have demonstrated an association of elevated MMP-9 levels with poor outcomes in stroke patients. In addition to the exacerbation of blood-brain barrier dysfunction after injury ischemic injury/re-perfusion, MMP-9 is also known to be involved in the mechanism of the central depression within acute stroke patients, and it contributes to the destruction of brain cells, thus aggravating the incidence of brain oedema [19]. The central depression is characterised by the neuronal and glial depolarisation, followed by an increased expression of MMP-9 after 3-6 hours. There is also evidence that shows the detrimental role of MMP-9, which leads to the expansion of brain injury after focal ischemia [23]. The increased activity of MMP-9 is characterised by the simultaneous reduction in the extracellular matrix changing the adhesive contact of neuronal cells to the extracellular matrix and by events that underlie their contributions to neuronal degeneration in the ischemic penumbra. This lead to migration of neutrophils to brain parenchyma and stimulates another release of MMP-9 of resident brain cells (neurons and glial cells) which resulted in apoptosis of these cells [24]. A recent study demonstrated that MMP-9 could directly trigger anoikis, such as neuronal death due to the occurrence of signal interference between cells and the matrix [13]. Indeed, activation of MMP-9 is associated with the size of the brain infarct. Also, levels of pro-MMP-9 in plasma and levels of activated MMP-9 in the murine cerebral tissue increased after 24-hours of permanent occlusion of the middle cerebral artery. The increment of pro-MMP-9 levels in plasma at 24 hours was associated with the infarct size [25]. In human study, increased MMP-9 plasma level correlated with infarct volume increment at baseline (0-6th hour), 12, 24, and 48th hour after stroke and correlated with higher NIHSS scores at 12, 24 and 48th hour [26]. Another study showed increased MMP-9 plasma level on admission was positively correlated with NIHSS score after 1 month and 12% increased the risk for major disability, and 29% increased the risk for death in the 3-month interval after stroke [27] [28]. It is worth to mention that these 2 studies did not find any significant correlation between blood glucose and MMP-9 plasma level, showing that another mechanism besides hyperglycemia could affect the association between MMP-9 levels and stroke outcome [27] [28].

Researchers are attempting to confirm a link between increased levels of MMP-9 with the poor outcomes of ischemic stroke. However, we did not observe any significant correlation between MMP-9 levels and the stroke outcomes as assessed with the GMSS ($p = 0.214$). An analysis using the Mann-Whitney test to see any significant difference in clinical outcomes between patients with MMP-9 levels above and below the cut-off point also showed no significant difference. This is in contrast to results of other studies that have been previously described. The difference could be partly explained by one of the limitations of this study, i.e., no stratification of patients based on their medical history of diabetes mellitus. Previous studies have shown that an up-regulation of MMP-9 activity contributes to the exacerbation of vascular damage in diabetic patients, but not in patients with acute hyperglycemia [29]. This vascular damage disrupted the blood-brain barrier and led to an unfavourable outcome in diabetic patients [30].

We acknowledge several limitations of this study: (1) no stratification of patients based on their medical history of diabetes mellitus; (2) no stratification of patients by the subtype of ischemic stroke, such as atherosclerosis in large arteries or cardiac embolism; (3) no distinction of size and location of the infarct's lesion and the involvement of cerebral arteries; and (4) no significant difference on comorbidity factors between the hyperglycemic and the non-hyperglycemic subjects was observed. Based on these limitations, we recommend conducting a more comprehensive study to improve these weaknesses.

We conclude that based on the calculated cut-off point (600.99 ng/mL), the proportion of higher MMP-9 levels were significantly more in the hyperglycemic than in the non-hyperglycemic group of acute ischemic stroke patients.

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References

1. A. D. Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2012; 35:S64-71. https://doi.org/10.2337/dc12-s064 PMid:22187472 PMCid:PMC3632174

2. Williams LS, Rotich J, Qi R, Fineberg N, Espay A, Bruno A, Fineberg SE, Tierney WR. Effects of admission hyperglycemia on mortality and costs in acute ischemic stroke. Neurol. 2002; 59:67-71. https://doi.org/10.1212/WNL.59.1.67

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

4. Bevers MB, Vaishnav NH, Pham L, Battey TW, Kimberly WT. Hyperglycemia is associated with more severe cytotoxic injury after stroke. J Cereb Blood Flow Metab. 2016; 37:2577-83. https://doi.org/10.1177/0271678X16671730 PMid:27671250 PMCid:PMC5531353

5. Uemura S, Matsushita H, Li W, Glassford AJ, Asagami T, Lee KH, Harrison DG, Tsao PS. Diabetes mellitus enhances vascular matrix metalloproteinase activity: role of oxidative stress. Circ Res. 2001; 88:1291-8. https://doi.org/10.1161/hh1201.092042 PMid:11420306

6. Aljada A, Ghanim H, Mohanty P, Syed T, Bandyopadhyay A, Dandona P. Glucose intake induces an increase in activator protein 1 and early growth response 1 binding activities, in the expression of tissue factor and matrix metalloproteinase in mononuclear cells, and in plasma tissue factor and matrix metalloproteinase concentrations. Am J Clin Nutr. 2004; 80:51-7. https://doi.org/10.1093/ajcn/80.1.51 PMid:15213027

7. Zhao BQ, Tejima E, Lo EH. Neurovascular proteases in brain injury, hemorrhage and remodeling after stroke. Stroke. 2007; 38:748-52. https://doi.org/10.1161/01.STR.0000253500.32979.d1 PMid:17261731

8. Montaner J, Alvarez-Sabín J, Molina C, Anglés A, Abilleira S, Arenillas J, González MA, Monasterio J. Matrix metalloproteinase expression after human cardioembolic stroke: temporal profile and relation to neurological impairment. Stroke. 2001; 32:1759-66. https://doi.org/10.1161/01.STR.32.8.1759 PMid:11486102

9. Abdelnaseer M, Elfayomi N, Hassan E, Kamal M, Hamdy A, Elsawy E. Serum matrix metalloproteinase-9 in acute ischemic stroke and its relation to stroke severity. Egypt J Neurol Psychiatry Neurosurg. 2015; 52:274-8. https://doi.org/10.4103/1110-1083.170661

10. Barr TL, Latour LL, Lee KY, Schaewe TJ, Luby M, Chang GS, El-Zammar Z, Alam S, Hallenbeck JM, Kidwell CS, Warach S. Blood brain barrier disruption in humans is independently associated with increased matrix metalloproteinase-9. Stroke. 2010; 41:123-8. https://doi.org/10.1161/STROKEAHA.109.570515 PMid:20035078 PMCid:PMC2827673

11. Hao Y, Tian S, Sun M, Zhu Y, Nie Z, Yang, S. Association between matrix metalloproteinase gene polymorphisms and development of ischemic stroke. Int J Clin Exp Pathol. 2015; 11647-52. PMid:26617904 PMCid:PMC4637720

12. Buraczynska K, Kurzepa J, Ksiazek A, Buraczynska M, Rejdak K. Matrix metalloproteinase-9 (MMP-9) gene polymorphism in stroke patients. Neuromolecular Med. 2015; 17:385-90. https://doi.org/10.1007/s12017-015-8367-5 PMid:26330106 PMCid:PMC4643105

13. Gu Z, Kaul M, Yan B, Kridel SJ, Cui J, Strongin A, Smith JW, Liddington RC, Lipton SA. S-nitrosylation of matrix metalloproteinases: signaling pathway to neuronal cell death. Science. 2002; 297:1186-90. https://doi.org/10.1126/science.1073634 PMid:12183632

14. Chaturvedi M, Kaczmarek L. MMP-9 inhibition: a therapeutic strategy in ischemic stroke. Mol Neurobiol. 2014; 49:563-73. https://doi.org/10.1007/s12035-013-8538-z PMid:24026771 PMCid:PMC3918117

15. Pöllänen PJ, Karhunen PJ, Mikkelsson J, Laippala P, Perola M, Penttilä A, Mattila KM, Koivula T, Lehtimäki T. Coronary artery complicated lesion area is related to functional polymorphism of matrix metalloproteinase 9 gene: an autopsy study. Arterioscler Thromb Vasc Biol. 2001; 21:1446-1450. https://doi.org/10.1161/hq0901.095545 PMid:11557670

16. Lamsudin R. Reliability of Gadjah Mada Stroke Scale (GMSS) in stroke patients. In: PERDOSSI. Buku Abstrak Musyawarah Kerja dan Pertemuan Ilmiah Tahunan Perdossi, PERDOSSI: Malang, Indonesia, 1998.

17. Kamada H, Yu F, Nito C, Chan PH. Influence of hyperglycemia on oxidative stress and MMP-9 activation after focal cerebral ischemia/reperfusion in ats: relationship to blood-brain barrier dysfunction. Stroke. 2007; 38:1044-9. https://doi.org/10.1161/01.STR.0000258041.75739.cb PMid:17272778 PMCid:PMC1828129

18. Sapojnikova N, Kartvelishvili T, Asatiani N, Zinkevich V, Kalandadze I, Gugutsidze D, Shakarishvili R, Tsiskaridze A. Correlation between MMP-9 and extracellular cytokine HMGB1 in prediction of human ischemic stroke outcome. Biochim Biophys Acta. 2014; 1842:1379-84. https://doi.org/10.1016/j.bbadis.2014.04.031 PMid:24815357

19. Gursoy-Ozdemir Y, Qiu J, Matsuoka N, Bolay H, Bermpohl D, Jin H, Wang X, Rosenberg GA, Lo EH, Moskowitz MA. Cortical spreading depression activates and upregulates MMP-9. J Clin Invest. 2004; 113:1447-55. https://doi.org/10.1172/JCI200421227 PMid:15146242 PMCid:PMC406541

20. Hsieh HL, Chi PL, Lin CC, Yang CC, Yang CM. Up-regulation of ROS-dependent matrix metalloproteinase-9 from high-glucose-challenged astrocytes contributes to the neuronal apoptosis. Mol Neurobiol. 2014; 50:520-33. https://doi.org/10.1007/s12035-013-8628-y PMid:24395134

21. Tsai WC, Liang FC, Cheng JW, Lin LP, Chang SC, Chen HH, Pang JH. High glucose concentration up-regulates the expression of matrix metalloproteinase-9 and -13 in tendon cells. BMC Musculoskelet Disord. 2013; 14:255. https://doi.org/10.1186/1471-2474-14-255 PMid:23981230 PMCid:PMC3765930

22. Sachwani GR, Jaehne AK, Jayaprakash N, Kuzich M, Onkoba V, Blyden D, Rivers EP. The association between blood glucose levels and matrix-metalloproteinase-9 in early severe sepsis and septic shock. J Inflamm. 2016; 13:1-8. https://doi.org/10.1186/s12950-016-0122-7 PMid:27110221 PMCid:PMC4840979

23. Planas AM, Solé S, Justicia C. Expression and activation of matrix metalloproteinase-2 and -9 in rat brain after transient focal cerebral ischemia. Neurobiol Dis. 2001; 8:834-46. https://doi.org/10.1006/nbdi.2001.0435 PMid:11592852

24. Turner RJ, Sharp FR. Implications of MMP9 for blood brain barrier disruption and hemorrhagic transformation following ischemic stroke. Front Cell Neurosci. 2016; 10:1-13. https://doi.org/10.3389/fncel.2016.00056 PMid:26973468 PMCid:PMC4777722

25. Park KP, Rosell A, Foerch C, Xing C, Kim WJ, Lee S, Opdenakker G, Furie KL, Lo EH. Plasma and brain matrix metalloproteinase-9 after acute focal cerebral ischemia in rats. Stroke. 2009; 40:2836-42. https://doi.org/10.1161/STROKEAHA.109.554824 PMid:19556529 PMCid:PMC3712850

26. Demir R, Ulvi H, Ozel L, Özdemir G, Güzelcik M, Aygül R. Relationship between plasma metalloproteinase-9 levels and volume and severity of infarct in patients with acute ischemic stroke. Acta Neurol Belg. 2012; 112:351-6. https://doi.org/10.1007/s13760-012-0067-4 PMid:22581515

27. Abdelnaseer MM, Elfauomy NM, Esmail EH, Kamal MM, Elsawy EH. Matrix metalloproteinase-9 and recovery of acute ischemic stroke. J Stroke Cerebrovasc Dis. 2017; 26:733-40. https://doi.org/10.1016/j.jstrokecerebrovasdis.2016.09.043 PMid:28063771

28. Zhong C, Yang J, Xu T, Xu T, Peng Y, Wang A, Wang J, Peng H, Li Q, Ju Z, Geng D, Zhang Y, He J; CATIS Investigators. Serum matrix metalloproteinase-9 levels and prognosis of acute ischemic stroke. Neurol. 2017; 89:805-12. https://doi.org/10.1212/WNL.0000000000004257 PMid:28747453 PMCid:PMC5580861

29. Elgebaly MM, Ogbi S, Li W, Mezzetti EM, Prakash R, Johnson MH, Bruno A, Fagan SC, Ergul A. Neurovascular injury in acute hyperglycemia and diabetes: a comparative analysis in experimental stroke. Transl Stroke Res. 2011; 2:391-8. https://doi.org/10.1007/s12975-011-0083-3 PMid:21909340 PMCid:PMC3169178

30. Yu X, Xu X, Jackson A, Sun J, Huang P, Mao Y, Chen Z, Lou M, Jiang Q, Zhang M. Blood brain barrier disruption in diabetic stroke related to unfavorable outcome. Cerebrovasc Dis. 2016; 42:49-56. https://doi.org/10.1159/000444809 PMid:26986824