Bioengineering Research

Impact of Pre-stroke Metformin Use on Prognosis of Ischemic Stroke; A Pilot Study

Sara Esmaeili [1], Faeze Abbasi [2], Mohammad hossein Abbasi [3], Azadeh Eshraghi [4], Zahra Mirzaasgari [1]

[1]Clinician Scientist Current Trainee, Firoozgar Hospital, Student Research Committee,Iran University of Medical Sciences, Tehran, Iran.
[2]Firoozgar Hospital, Student Research Committee, Iran University of Medical Sciences. Tehran, Iran.
[3]Firoozgar Hospital, Student Research Committee, Iran University of Medical Sciences. Tehran, Iran.
[4]Department of Clinical Pharmacy, Faculty of Pharmacy, Iran University of Medical Sciences, Tehran, Iran.
[5]Assistant Professor of Neurology , Iran University of Medical Sciences, Tehran, Iran
Correspondence to: Mirzaasgari Z. (E-mail: mirzaasgari@gmail.com)

Abstract:

Introduction: Ischemic stroke can arise from many atherosclerotic events including diabetes mellitus, a worldwide challenge now a day. Many factors have been shown to be effective on improvement of clinical prognosis in diabetic patients with stroke including good glucose control achieves most commonly by Metformin consumption. Metformin is shown previously to decrease the rate of incidence of stroke in diabetic patients, but its effect on clinical prognosis and severity of ischemic stroke in diabetic patients who involve by ischemic stroke has not been evaluated unless in a few researches, making the current research purpose.

Method: 40 Diabetic patients who were involved by ischemic stroke were enrolled in our study according to inclusion and exclusion criteria, placed equally 20 patients in each of the groups of our research, the former consisted of diabetic patients who were under glucose control by Metformin and the latter consisted of diabetic patients who were receiving other medications else than Metformin. At the day of stroke and at the end of a three months course, while patients were continuing the previous antidiabetic medical regimens during this course, clinical outcome and severity of diabetic stroke patients evaluated by MRSA and NIHSS respectively.

Results: results showed no statistically significant difference between Metformin consumers and non-consumers in both initial and final MRS scores, means that there is no correlation between Metformin consumption and a better prognosis in diabetic patients with stroke. RTPA consumption were of value for improvement in patients final MRS score means a more favorable outcome.

Conclusion: Although Metformin therapy is known as a protective factor in diabetic patients decreasing the risk of ischemic stroke, probably by maintaining the normoglycemic state in patients, despite some previously performed studies results, here we have not found any clinically significant efficacy of Metformin in improvement of clinical outcome and lowering stroke severity in diabetic patients involved by ischemic brain stroke.

Keywords: stroke; diabetes; Metformin; MRS, NIHSS

Received: 7 December 2019, **Accepted**: 25 December 2019

DOI: 10.22034/jbr.2019.97272

Tissues & Biomaterials Research Group

1. Introduction

Diabetes mellitus (DM) type 2 is an insulin resistance syndrome, arises from many factors including sedentary life style, obesity, genetics and etc. [1]. DM type II is a known risk factor of cardiovascular complications due to increased risk of thromboembolic events and subsequent ischemic stroke of brain and heart [2-4]; furthermore, previous studies have shown DM as a risk factor for evidence of atherosclerosis and platelet aggregation in which subsequently leading to ischemic brain stroke due to thrombotic events accompanied by higher rate of hemodynamic instability in stroke patients [4-6].

Many factors are involved in the clinical prognosis and outcome in patients with ischemic stroke including good glucose control in diabetic patients, predicts a more favorable outcome with lesser complications of stroke [7]. Poor outcome indicators in diabetic patients who involve by ischemic brain stroke are comprised of higher age, living alone, atrial fibrillation, heart failure, dementia, hyperglycemia and a more severe stroke [8-11]. A previous study showed decreased risk of stroke in diabetic patients who consume Metformin in comparison to diabetics who receive other antidiabetic medications [12]. Metformin is also capable of neuroprotective and angiogenetic effects suggesting its value in improvement of clinical prognosis in diabetic patients involved by ischemic stroke [13].

Metformin is a commonly used antidiabetic medication with favorable glucose control in patients with DM type II as the first line therapy. This medication is a derivative of European Galega officinalis plant [14]. Metformin has been shown to decrease the risk of death in diabetic patients from all causes consisted of heart diseases and brain ischemic stroke; indicated by United Kingdom Prospective Study (UKPDS) [15].

Mima et al. have shown the efficacy of Metformin in decrease the neurologic severity and improve the clinical outcome in diabetic patients with brain stroke leading to decreased subsequent neurologic disability [16]. Li et al. have shown the neuroprotective effect of Metformin in an experimental study on male mouse stroke models received Metformin before stroke in which decreased the rate of stroke induced lactate generation by repression of activation of stroke induced AMPK factor [13], [17]. Furthermore, some other experimental studies have shown decreased ischemic neuronal injuries when stroke models were given Metformin two weeks before induction of a global cerebral ischemia focused at hippocampus [18], [19]. Jiang et al. indicated the neuroprotective effect of Metformin when be given 24 hours before ischemic stroke event [20]. Another experimental study showed improvement in vascular remodeling and decrease in severity of hemorrhagic transformation in stroke models when they were given Metformin four weeks in advance of ischemic brain stroke [21].

Although it has been shown previously that Metformin is potential in decrease the rate of stroke in diabetic patients, its effect on clinical prognosis and severity of stroke has not evaluated unless in a few previous researches, making the purpose of our study to evaluate the effect of Metformin on clinical outcome and severity of stroke in diabetic patients in a case control study after a three month course.

Method:

40 diabetic patients with stroke were enrolled in our study according to inclusion and exclusion criteria, consisted of 20 patients in each group; the former was comprised of diabetic patients who were consuming Metformin since at least 3 weeks in advance of stroke time and the latter consisted of diabetic patients who were under control by else medications than Metformin. Evidence of stroke approved by imaging studies in which were suggestive of ischemic stroke. Inclusion criteria for sampling were comprised of diabetic patients with ischemic stroke referred to Firoozgar hospital and signed the consent paper. Exclusion criteria of this study were consisted of patients with diabetic nephropathy (stage 4 renal failure or creatine clearance lower than 30 ml/min/1.73 m2), poor glucose control by metformin and MRS score over 2 prior to stroke.

At the time of stroke and after three months, patients in both groups assessed by Modified Rankin Score

(MRS) and National Institutes of Health Stroke Scale (NIHSS). Then, measures of Metformin receivers group compared to the measures of non-Metformin receivers in a case control study to evaluate the effect of metformin on outcome (assessed by MRS) and severity (assessed by NIHSS) in diabetic patients with ischemic stroke. Desired NIHSS measure as low severity defined as the score lower than 3 and desired MRS measure as good prognosis and outcome defined as the score equal or lower than 2.

Statistical analysis of measures was performed by SPSS version 22. Descriptive statistics of quantitative data were defined by mean and standard deviation or median and interquartile ranges (first and third quartiles). Descriptive statistics of qualitative data were defined by prevalence (percent). In each group of patients, for comparison of outcome before and after the mentioned three months, paired sample T-test or its non-parametric equivalent test, Wilcoxon test were employed. In order to compare qualitative data between two groups of our study, Chi-square test was used and fisher's exact test also performed in those cases in which the required statistical assumptions were not met for Chi-square test. Analysis of variances (ANOVA test) performed to compare quantitative data between groups of patients over 2 in number. P-value in this study were assumed <0.05 as statistically significant measure.

Results:

Analyzing by Chi-square test, revealed no statistically significant correlation between consumption of Metformin and final MRS score (P-value > 0.05 with CI of 95%); Fisher's exact test also was performed due to presence of lower than 5 sample in a cell, revealed no statistically significant correlation between Metformin consumption and final MRS score (P-value = 0.2 by CI of 95%).

Assessing the correlation between initial MRS score with Metformin consumption by comparison of Metformin consumers and non-consumers by Chi-square test, there has not been a statistically significant correlation between Metformin consumption and initial MRS score (P-value = 0.86); Ficher's exact test also revealed no correlation (P-value = 0.97).

Comparing the final MRS score by analyzing by Chi-square test and then Ficher exact test, between groups of patients who received RTPA and were consuming Metformin with those patients who didn't received RTPA and were not using Metformin, both again revealed no statistically significant correlation between their final MRS scores (P-value = 0.054 with CI of 95%).

Comparing the final MRS scores by Chi-square test, between groups of patients who received RTPA with those who have not, revealed statistically significant differences indicated the positive effect of RTPA in stroke prognosis (P-value = 0.01).

Analyzing the correlation between HbA1c level and final MRS score by ANOVA analysis, revealed no statistically significant correlation (P-value=0.1 by CI of 95%).

Discussion:

Despite previously indicated protective effect of Metformin in involvement of diabetic patients with brain ischemic stroke and also more favorable clinical outcome of stroke in diabetic patients who were consuming Metformin in comparison to patients under control by other antidiabetic medications, here we found no statistically significant correlation between consumption of Metformin and a more favorable clinical outcome or lower severity of stroke in diabetic patients. This opposite result may be due to low sample size of patients were enrolled in our study. Another reason of this negative result could be due to short term follow up of patients for the second assessment.

There have been also other opposing results were shown by researches such as ours and also by Chen et al. who indicated the increased risk of Alzheimer's disease in patients received Metformin, despite proven neuroprotective effect suggested for Metformin previously [22].

Conclusion:

Although Metformin is potential in decreasing the rate of incidence of stroke in diabetic patients, but according to the findings of our study this antidiabetic medication is of no clinically significant value in improve the outcome and decrease the severity of stroke.

Acknowledgement:

we would thank attendings, residents, nurses and all staff of Firoozgar hospital neurology ward for their endless effort for improvement of patients and for all their support.

Conflict of interest:

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

References

[1] Kendall DM, Harmel AP. The metabolic syndrome, type 2 diabetes, and cardiovascular disease: understanding the role of insulin resistance. Am J Manag Care 2002;8(20 Suppl):S635–S653.

[2] Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 1993;16(2): 434–444. [PubMed: 8432214]

[3] Folsom AR, Rasmussen ML, Chambless LE, Howard G, Cooper LS, Schmidt MI, Heiss G. Prospective associations of fasting insulin, body fat distribution, and diabetes with risk of ischemic stroke. The Atherosclerosis Risk in Communities (ARIC) study investigators. Diabetes Care 1999;22:1077–1083. [PubMed: 10388971]

[4] Kain K, Catto AJ, Grant PJ (2003) Associations between insulin resistance and thrombotic risk factors in high-risk South Asian subjects. Diabet Med 20:651–655

[5] Perez PM, Moore-Carrasco R, Gonzalez DR, Fuentes EQ, Palomo IG (2012) Gene expression of adipose tissue, endothelial cells and Metab Brain Dis platelets in subjects with metabolic syndrome (review). Mol Med Rep 5:1135–1140

[6] Vazzana N, Ranalli P, Cuccurullo C, Davi G (2012) Diabetesmellitus and thrombosis. Thromb Res 129:371–377

[7] Nair SS, Sylaja PN, Sreedharan SE, Sarma S. Maintenance of normoglycemia may improve outcome in acute ischemic stroke. Annals of Indian Academy of Neurology. 2017 Apr;20(2):122.

[8] Zhao L, Wang L, Lu M, Hu W, Xiu S. Hyperglycemia is associated with poor in-hospital outcome in elderly patients with acute ischemic stroke. Medicine. 2019 Aug;98(31).

[9] Mima Y, Kuwashiro T, Yasaka M, Tsurusaki Y, Nakamura A, Wakugawa Y, Okada Y. Impact of metformin on the severity and outcomes of acute ischemic stroke in patients with type 2 diabetes mellitus. Journal of Stroke and Cerebrovascular Diseases. 2016 Feb 1;25(2):436-46.

[10] Appelros P, Nydevik I, Viitanen M. Poor outcome after first-ever stroke: predictors for death, dependency, and recurrent stroke within the first year. Stroke. 2003 Jan 1;34(1):122-6.

[11] Appelros P, Nydevik I, Seiger A, Terént A. Predictors of severe stroke: influence of preexisting dementia and cardiac disorders. Stroke. 2002 Oct 1;33(10):2357-62.

[12] Cheng YY, Leu HB, Chen TJ, Chen CL, Kuo CH, Lee SD, Kao CL. Metformin-inclusive therapy reduces the risk of stroke in patients with diabetes: a 4-year follow-up study. Journal of Stroke and Cerebrovascular Diseases. 2014 Feb 1;23(2):e99-105.

[13] Jin Q, Cheng J, Liu Y, Wu J, Wang X, Wei S, Zhou X, Qin Z, Jia J, Zhen X. Improvement of functional recovery by chronic metformin treatment is associated with enhanced alternative activation of microglia/macrophages and increased angiogenesis and neurogenesis following experimental stroke. Brain, behavior, and immunity. 2014 Aug 1;40:131-42.

[14] Arbeláez-Quintero I, Palacios M. To use or not to use metformin in cerebral ischemia: a review of the application of metformin in stroke rodents. Stroke research and treatment. 2017;2017.

[15] S. Genuth, R. Eastman, R. Kahn et al., "Implications of the United Kingdom Prospective Diabetes Study," Diabetes Care, vol. 25, no. 1, pp. S28–S32, 2002.

[16] Mima Y, Kuwashiro T, Yasaka M, Tsurusaki Y, Nakamura A, Wakugawa Y, Okada Y. Impact of metformin on the severity and outcomes of acute ischemic stroke in patients with type 2 diabetes mellitus. Journal of Stroke and Cerebrovascular Diseases. 2016 Feb 1;25(2):436-46.

[17] Li J., Benashski S.E., Venna V.R., McCullough L.D. Effects of metformin in experimental stroke. Stroke. 2010;41(11):2645–2652. doi: 10.1161/ STROKEAHA. 110.589697

[18] Ashabi G., Khalaj L., Khodagholi F., Goudarzvand M., Sarkaki A. Pre-treatment with metformin activates Nrf2 antioxidant pathways and inhibits inflammatory responses through induction of AMPK after transient global cerebral ischemia. Metab. Brain Dis. 2014

[19] Ashabi G., Khodagholi F., Khalaj L., Goudarzvand M., Nasiri M. Activation of AMP-activated protein kinase by metformin protects against global cerebral ischemia in male rats: interference of AMPK/PGC-1α pathway. Metab. Brain Dis. 2014;29(1):47–58. doi: 10.1007/s11011-013-9475-2.

[20] Jiang T., Yu J.T., Zhu X.C., Wang H.F., Tan M.S., Cao L., Zhang Q.Q., Gao L., Shi J.Q., Zhang Y.D., Tan L. Acute metformin preconditioning confers neuroprotection against focal cerebral ischaemia by pre-activation of AMPK-dependent autophagy. Br. J. Pharmacol.2014;171(13):3146–3157.doi: 10.1111/bph.12655.

[21] Elgebaly M.M., Prakash R., Li W., Ogbi S., Johnson M.H., Mezzetti E.M., Fagan S.C., Ergul A. Vascular protection in diabetic stroke: role of matrix metalloprotease-dependent vascular remodeling. J. Cereb. Blood Flow Metab. 2010;30(12):1928–1938. doi: 10.1038/jcbfm.2010.120

[22] Y. Chen, K. Zhou, R. Wang et al., "Antidiabetic drug metformin (GlucophageR) increases biogenesis of Alzheimer's amyloid peptides via up-regulating BACE1 transcription," Proceedings of the National Academy of Sciences of the United States of America, vol. 106, no. 10, pp. 3907–3912, 2009.