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ORIGINAL ARTICLE **ÖZGÜN ARAŞTIRMA**

THE EFFECT OF METFORMIN THERAPY ON SEVERITY AND PROGNOSIS IN ACUTE ISCHEMIC STROKE

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ABSTRACT

INTRODUCTION: Diabetes mellitus (DM) is an important risk factor for ischemic stroke. The results for the prevention of stroke recurrence with antidiabetic therapy have been contraversial. The some of data may indicate the positive effects of metformin treatment on stroke recurrence, stroke severity and prognosis. The aim of this study was to investigate the effect of metformin therapy usage on severity and pronosis of acute ischemic stroke.
METHODS: The consecutive patients who were admitted to acute ischemic stroke with DM and accepted to participate in the study from January 2017 to April 2019 were evaluated, prospectively. The demographic data, risk factors, NIHSS scores at admission, etiologic stroke subtypes and mRS scores at discharge were recorded. The patients were divided into two groups. The patients with usage metformin or metformin plus other antidiabetic therapy were in group 1 and the patients taking antidiabetic therapy other than metformin or patients with type 2 DM receiving no antidiabetic therapy were in group 2.
RESULTS: Of the 70 patients included in the study, 42 patients (60%) were in group 1 and 28 patients (40%) were in group 2. There was not any significant difference between the groups of severity and pronosis of acute ischemic stroke ($p>0.05$).
DISCUSSION AND CONCLUSION: The usage of metformin and other antidiabetic therapy had no effect on the severity and prognosis of ischemic stroke. However, further controlled studies are needed with larger samples.
Keywords: Metformin, acute ischemic stroke, severity of stroke, pronosis.

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METFORMİN KULLANIMININ AKUT İSKEMİK İNMEDE ŞİDDET VE PROGNOZ ÜZERİNE ETKİSİ

ÖZ

GİRİŞ ve AMAÇ: Diabetes mellitus (DM), iskemik inme için önemli bir risk faktörüdür. Antidiabetik tedavi ile inme tekrarının önlenmesine yönelik çelişkili sonuçlar vardır. Metformin tedavisinin inme tekrarı, inme şiddeti ve prognozu üzerine olumlu etkilerini işaret edebilecek bazı veriler mevcuttur. Bu çalışmanın amacı oral antidiabetik metforminin akut iskemik inme şiddeti ve seyri üzerine etkisini araştırmaktır.

YÖNTEM ve GEREÇLER: Ocak 2017 ve Nisan 2019 tarihleri arasında nöroloji kliniğine akut iskemik inme tanısı ile yatan ve çalışmaya katılmayı kabul eden DM hastalarının prospektif olarak alınmıştır. Demografik bilgileri, risk faktörleri, muayene bulguları, laboratuvar ve radyolojik tetkikleri, inme etyolojileri ve taburculuk sırasında klinik seyirleri kaydedilmiştir. Hastalar iki gruba ayrılmıştır. Grup 1'de metformin veya metforminle beraber diğer antidiabetik ilaç kullanan tip 2 DM hastaları ve grup 2'de metformin dışında antidiabetik ilaç kullanan veya hiçbir antidiabetik ilaç almayan tip 2 DM hastaları yer almıştır.

BULGULAR: Bu çalışmaya 70 hasta alınmıştır; grup 1 de 42 hasta (%60), grup 2'de 28 hasta (%40) hasta vardır. Gruplar arasında iskemik inme şiddeti ve prognozu açısından istatistiksel olarak anlamlı bir fark görülmemiştir ($p>0.05$).

TARTIŞMA ve SONUÇ: İnme öncesinde metformin kullanımının diabetik hastalarda iskemik inme şiddeti ve prognozu üzerine etkisi bulunmamıştır. Ancak daha fazla sayıda hastayı içeren çok merkezli yeni çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Metformin, akut iskemik inme, inme şiddeti, prognoz.

INTRODUCTION

Macroangiopathy is a major complication of diabetes mellitus (DM) and is the leading cause of morbidity and mortality. Diabetes accelerates the progression of atherosclerotic plaques. Oxidative stress mediates this process along with vascular cell dysfunction, which results in plaque erosion and rupture and which is a key factor in inflammatory events. Epidemiological studies also show that postprandial hyperglycemia is strongly associated with stroke and stroke-related mortality. Postprandial hyperglycemia may contribute to vascular damage through various mechanisms such as endothelial dysfunction, atherosclerosis, oxidative stress, inflammation, and hypercoagulability (1,2).

There are contradictory results for the prevention of recurrence of stroke with antidiabetic treatment (3-27). There are some data that may indicate the positive effects of Metformin treatment on stroke recurrence, stroke severity, and prognosis (1-3,14,22).

Metformin is an antihyperglycemic agent widely used in the treatment of DM. Metformin is one of the drugs in the biguanide group that increases insulin sensitivity. Metformin has been suggested to have antioxidant properties that contribute to the vasculoprotective effects observed in several epidemiological studies as well as its glucose-lowering effects. Metformin has a direct cleansing effect against in vitro-produced free radicals and reduces intracellular production of reactive oxygen species (ROS) in aortic endothelial cells through both nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and decrease in the mitochondrial respiratory pathway. Free oxygen radicals are known to cause many harmful cardiovascular effects by increasing the oxidation of low-weight lipoproteins; Metformin cleans oxygen radicals (28).

This study aims to investigate the effect of Metformin on the severity and course of acute ischemic stroke.

METHODS

This study was conducted in accordance with the Helsinki Declaration ethical standards and approved by the Ankara University Faculty of Medicine Clinical Studies Ethics Committee (Number: 11-607-17, Date: 12.06.2017).

70 type-2 DM patients who wanted to participate in the study and were diagnosed according to the American Diabetes Society criteria of the 293 patients admitted to the neurology clinic with the diagnosis of acute ischemic stroke between January 2017 and April 2019 were prospectively included in this study (29). 223 patients who did not want to participate in the study, had a hemorrhagic stroke, type-1 DM, severe renal failure, and severe deterioration in daily life activities before stroke (modified Rankin scale (mRS) score >=3) were not included in this study. An informed voluntary consent form was signed and obtained from all patients.

Age, gender, and clinical histories of all patients were recorded at the time of admission. The history of hypertension (HT), hyperlipidemia (HL), atrial fibrillation (AF), coronary artery disease (CAD), congestive heart failure (CHF), previous stroke and/or transient ischemic attack (TIA), smoking and alcohol use, all of which are risk factors for stroke, were questioned. Previous medications, especially antiplatelet, anticoagulant, antilipidemic, antidiabetic, and antihypertensive medications, have been recorded. Physical and neurological examinations of the patients were performed, and their blood pressure was measured at the time of admission. Then, the National Stroke Health Scale (NIHSS) scores, body mass index (BMI) at the first admission were calculated. Complete blood count, fasting blood glucose (FBG), fasting blood glucose (FBG), kidney function tests and electrolytes (BUN, creatine, Na, K, GFR), HbA1c, lipid profile, computed brain tomography (CBT), electrocardiography (ECG), diffusion-weighted magnetic resonance imaging (DW-MRI), and brain-neck computed tomography angiography (CTA), or carotid and vertebral Doppler ultrasonography (DUS), or brain-neck magnetic resonance angiography (MRA), 24-hour ECG monitoring, transthoracic echocardiography (TTE), and/or transesophageal echocardiography (TEE) results of all examined patients were recorded.

Automated CCS (Causative Classification System) was used to determine the etiological type of ischemic stroke (30). The mRS scores at the time of discharge were calculated. The patients were divided into 2 groups. Group 1 included type-2 DM patients taking metformin or metformin with other antidiabetic drugs, and Group 2 included type-2 DM patients taking antidiabetic drugs other than metformin or not taking any antidiabetic drugs. Groups were compared in terms of the severity and course of acute ischemic stroke.

Statistical Analysis: The data were analyzed in SPSS for Windows 15 package software. Descriptive statistics were shown as mean±standard deviation (SD) for variables with normal distribution, median (min-max) for variables with abnormal distribution, and nominal variables as the number of cases (%). The significance of the difference between the groups in terms of averages was investigated by the t-test and the significance of the difference in terms of median values was investigated by the Mann-Whitney U test after forming two groups. The significance of the difference between the groups in terms of averages was investigated by one-way analysis of variance and the significance of the difference in terms of median values was investigated by the Kruskal-Wallis test. The nominal variables were evaluated by Pearson's Chi-square or Fisher's exact test. The risk factors affecting the dependent variable were performed by Logistic Regression Analysis. The results for $p<0.05$ were considered statistically significant. The sample size required to determine whether the difference between the averages of the two groups with 0.80 power and 0.05 error margin is different from zero is 70.

RESULTS

A total of 70 patients admitted to our clinic with the diagnosis of acute ischemic stroke and type-2 DM were prospectively examined in this study. There were 42 patients (60%) in Group 1 (mean age:70.02±10.92, 57.1% female) and 28 patients (40%) in Group 2 (mean age 68.43±11.09, 42.9% female) (Table 1). The number of patients in Group 2 who did not take any antidiabetic drugs was 11.

There was no difference found between the two groups in terms of age, gender, previous diseases (hypertension, hyperlipidemia, atrial fibrillation, coronary artery disease, congestive heart failure, peripheral artery disease, transient ischemic attack (TIA), previous stroke, smoking, and alcohol use, blood pressure at the time of admission, and NIHSS and mRS values. Glycohemoglobin levels were higher in type-2 DM patients taking antidiabetic drugs other than Metformin or not taking any antidiabetic drugs whereas VLDL levels were higher in type-2 DM patients taking Metformin (Table 1). 13 (46.4%) patients in Group 2 were taking antiplatelet drugs (acetylsalicylic acid 8, clopidogrel 1, a combination of acetylsalicylic acid and clopidogrel 4), 2 (7.1%) patients were using anticoagulant drugs (warfarin 1, apixaban 1) whereas 24 (57.1%) patients in Group 1 were using antiplatelet drugs (acetylsalicylic acid 20, clopidogrel 2, a combination of acetylsalicylic acid and clopidogrel 2), 4 (9.5%) patients were using anticoagulant drugs (low molecular weight heparin 1, warfarin 1,

rivaroxaban 1, apixaban 1). There was no significant difference found between the two groups in terms of the use of antiplatelet drugs (p=0.77) and anticoagulants (p=0.73). There was no significant difference found between the groups in terms of etiology of ischemic stroke according to CCS (Table 2). There was no significant difference found between the groups in terms of the drugs taken by the patients at the time of the incidence of the stroke (Table 3). There was no difference between found the groups in terms of mean mRS score at the time of discharge. The recurrent stroke rates of the two groups during their hospitalization were also similar (Table 4).

Table 1. Demographic characteristics of the patients, mean blood pressure at the time of admission, and blood test results.

	Group 1 n=42	**Group 2 n=28**	**p**
Age, mean±SD	70.02± 1092	68.43± 11.09	0.97
Gender (M/F), n (%)	24 (57.1)/18 (42.9)	12 (42.9)/16 (51.1)	0.24
Hypertension, n (%)	34 (81)	26 (929)	0.16
Hyperlipidemia, n (%)	10 (238)	8 (286)	0.65
AF, n (%)	4 (9.5)	2 (7.1)	0.73
CAD, n (%)	17 (40.5)	11 (39.3)	0.92
CHF, n (%)	5 (11.9)	1 (3.6)	0.22
PAD, n (%)	2 (4.8)	2 (7.1)	0.67
Previous TIA, n (%)	4 (9.5)	0 (0)	0.93
Previous stroke, n (%)	7 (16.7)	4 (14.3)	0.79
Smoking, n (%)	10 (23.8)	13 (46.4)	0.048
Alcohol, n (%)	1 (2.4)	3 (10.7)	0.14
SBP at admission (mmHg), mean±SD	145.33± 2786	155.82± 33.24	0.46
DBP at admission (mmHg), mean±SD	80.71± 14.69	81.32± 17.83	0.11
FBS (mg/dL), mean±SD	144.94± 60.74	159.23± 87.31	0.33
HbA1C, n (%)	8.11± 1.78	8.84± 3.16	***0.003***
Total cholesterol (mg/dL), mean±SD	201± 60.6	184.86± 46.73	0.150
LDL (mg/dL), mean±SD	123.48± 41.28	113± 37.66	0.47
VLDL (mg/dL), mean±SD	35.12± 14.53	33.93± 18.8	***0.04***
HDL (mg/dL), mean±SD	38.55± 8.67	37.93± 9.97	0.22
Triglyceride (mg/dL), mean±SD	205.79± 165.49	170.39± 94	0.59
NIHSS score at admission, mean±SD	4.38± 377	4.89± 364	0.510

SD: standard deviation, F: Female, M: Male, AF: Atrial Fibrillation, CAD: Coronary artery disease, CHF: Congestive heart failure, PAD: Peripheral artery disease, TIA: Transient ischemic attack, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein, HDL: High-density lipoprotein, NIHSS: National Institutes of Health Stroke Scale, mRS: modified Rankin Scale, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, FBS: Fasting blood sugar.

Table 2. Etiological classification of ischemic stroke in patients included in the study.

CCS	**Group 1**	**Group 2**	**p**
Large artery atherosclerosis n (%)	17 (40.5)	11 (39.3)	
Cardio-aortic embolism n (%)	12 (28.6)	7 (25)	0.8
Small artery obstruction n (%)	7 (16.7)	5 (17.9)	
Other causes n (%)	2 (4.8)	0 (0)	
Undetermined, n (%)	4 (9.5)	5 (17.9)	

CCS: Causative Classification System.

Table 3. Drugs taken by the patients at the time of the incidence of the stroke.

Anti-DM drugs	**Group 1 n=42**	**Group 2 n=28**	**p**
Sulfonylureas, n (%)	18 (42.9)	5 (17.9)	0.029
Glinide group, n (%)	2 (48)	2 (71)	0.674
Thiazolidinediones (glitazones), n (%)	2 (48)	0	0.8
Alpha-glucosidase inhibitors, n (%)	2 (48)	0	0.24
Dipeptidyl peptidase-4 inhibitors, n (%)	4 (9.5)	4 (143)	0.54
Insulin preparations, n (%)	10 (23.8)	10 (35.7)	0.28
Antiplatelet drug, n (%)	24 (57.1)	13 (46.4)	0.38
Anticoagulant drug, n (%)	4 (95)	2 (71)	0.12
Antihypertensive drug, n (%)	29 (69)	20 (714)	0.83
Antihyperlipidemic drug, n (%)	6 (14.3)	4 (14.3)	1.0

Table 4. Discharge mRS score value and recurrent stroke rates.

	Group 1	Group 2	p
NIHSS score at discharge, mean±SD	1.95± 1.14	2.54± 1.4	0.697
Recurrent stroke, n (%)	7 (16.7)	3 (10.7)	0. 49

mRS: modified Rankin Scale, SD: standard deviation

DISCUSSION AND CONCLUSION

The effect of Metformin use on the severity and course of stroke was comparatively evaluated in all patients admitted to the neurology clinic with the diagnosis of acute ischemic stroke between January 2017 and April 2019 in this study. Metformin use prior to the first stroke did not have a different effect on stroke severity and prognosis than other antidiabetic drugs or patients who did not take any antidiabetic drugs. The recurrent stroke rates during hospitalization were also found to be similar.

14,856 type-2 DM patients were followed up for the following 4 years in a retrospective study conducted by Yuan-Yang Cheng et al., published in 2014. 994 (9.2%) of 10,857 patients taking Metformin developed a stroke whereas 701 (17.5%) of 3999 diabetic patients not taking Metformin had a stroke. The hazard ratio (HR) with Metformin use was found to be 0.468 considering other risk factors. Metformin treatment has been shown to prevent approximately half of the incidence of stroke during four years of follow-up in DM patients and its effect is more pronounced in high-risk patients in this study (24). Therefore, that Metformin should be the first agent to be preferred in primary prophylaxis of stroke has been suggested (14).

It was retrospectively evaluated whether there was a difference in the severity and course of stroke in acute ischemic stroke patients diagnosed with type-2 DM and taking Metformin (n=77), taking antidiabetic drugs other than Metformin (n=163), and taking no antidiabetic drugs at all in a study conducted by Yohei Mima et al., published in 2016. The severity of stroke was found to be significantly lower in patients taking Metformin compared to patients with acute ischemic stroke taking other antidiabetic drugs other than Metformin, and not taking any antidiabetic drugs in this study. Previous use of Metformin has been shown to improve functional outcomes only in patients with recurrence of stroke (22). It was observed in this prospective study that the use of Metformin after stroke did not provide an additional benefit in terms of stroke severity and stroke recurrence during hospitalization compared to other antidiabetic drugs or no antidiabetic drugs.

There are studies investigating the effects of oral antidiabetic drugs other than Metformin on prognosis and functional status after stroke. 100 patients diagnosed with type-2 DM were included in a prospective study published in 2015by Tziomolaset al. The severity, functional outcome, and mortality risk of acute ischemic stroke were evaluated in the group taking DPP-4 inhibitors (n=27) and taking antidiabetic drugs other than DPP-4 inhibitors (n=73). DPP-4 inhibitors have been shown to be associated with better functional outcomes and a lower risk of mortality in patients with acute ischemic stroke (15). It was not possible to evaluate the patients taking other antidiabetic drugs other than Metformin in different groups since the number of patients in our study was low.

Various limitations should be considered when interpreting the results of this study. Various stroke treatments and complications in the acute and chronic phases may have affected the prognosis of patients differently. The fact that our study was conducted in a single-center, that only inpatients were evaluated, and that the number of patients was low, constitute other weaknesses of our study.

In conclusion, the severity and prognosis of ischemic stroke were found to be similar between diabetic patients taking Metformin before the ischemic stroke and diabetic patients not taking Metformin in our study. Our results did not support the hypothesis that Metformin positively affects the severity and prognosis of acute ischemic stroke in patients with type-2 DM as previously suggested by some researchers. However, it is believed that there is a need for multicentered prospective studies in which the number of patients is higher.

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Ethics

Ethics Committee Approval: The study was approved by the Ankara University Faculty of Medicine Clinical Studies Ethics Committee (Number: 11-607-17, Date: 12.06.2017).

Informed Consent: The authors declared that informed consent was signed by all included patients.

Copyright Transfer Form: Copyright Transfer Form was signed by all authors.

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