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ORIGINAL ARTICLE

The effects of micro- and macrovascular diabetic complications on ischemic stroke in patients with type 2 diabetes mellitus

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ABSTRACT

Objectives: The present study aimed to examine the effects of diabetes complications on the ischemic stroke risk among patients with type 2 diabetes mellitus (T2DM).

Patients and methods: The medical records of all patients (n=5,468) who were admitted to a tertiary care hospital between January 1, 2021, and June 1, 2022, were retrospectively reviewed. Of 911 patients diagnosed with T2DM for at least two years, 37 patients with a history of hemorrhagic cerebrovascular disease were excluded. Consequently, the study was conducted with 874 patients (460 males, 414 females; mean age: 65.5±12.1 years; range, 39 to 92 years) with T2DM. Demographic data, presence of chronic disease other than diabetes, duration of diabetes, retinopathy, nephropathy, peripheral arterial disease, and diabetes medications were recorded. The patients were divided into two groups: those with and without a history of ischemic stroke. The two groups were compared in terms of demographic characteristics and diabetes complications.

Results: The prevalence of ischemic stroke was 18.6% (n=163). Patients with ischemic stroke were older than those without ischemic stroke, had longer diabetes durations, and had higher rates of hypertension, hyperlipidemia, and insulin use (p=0.001, p<0.001, p<0.001, p<0.001, and p<0.001, respectively). Diabetic retinopathy (41.7%), diabetic nephropathy (27.6%), and peripheral arterial disease (16.6%) were more commonly observed among patients with ischemic stroke compared to the others. Examining the parameters differing between the groups, diabetes duration, hypertension, insulin use, and peripheral arterial disease were found to be independent risk factors for ischemic stroke (p<0.001, p<0.001, p=0.001, and p=0.001, respectively).

Conclusion: Examining the relationship between diabetes complications and ischemic stroke risk from a broader perspective, the present study provided important implications for clinical management. Large-scale studies are needed in the future.

Keywords: Diabetes complications, ischemic stroke, risk factors, type 2 diabetes mellitus.

Type 2 diabetes mellitus (T2DM) is the most common type of diabetes (90%), and it is also an important public health problem with an increasing prevalence.[1,2] Sedentary life, unhealthy diet, increasing obesity, and social aging constitute the basis of the increase in the prevalence of diabetes. Diabetic individuals are more likely to have macrovascular complications, including coronary artery disease, peripheral arterial disease, and stroke.[3,4] In addition, it causes early microvascular complications, such as retinopathy, nephropathy, and neuropathy.[3,5] Previous studies reported a relationship between diabetes and stroke. In a study carried out between 1996 and 2006, it was reported that there was a 27% increase in comorbidity among stroke patients with diabetes.[6] Type 2 diabetes mellitus is one of the modifiable risk factors for ischemic stroke.[7] It is crucial to investigate preventable causes of ischemic stroke to develop strategies for targeted treatments.

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Studies on individuals with T2DM revealed a significant relationship between retinopathy and stroke.[8,9] Furthermore, there are studies indicating an increase in the risk of stroke due to diabetic nephropathy.[10-12] However, a cohort study carried out on diabetic patients with atrial fibrillation suggested that diabetic microvascular complications did not affect the risk of ischemic stroke.[13] Investigations on the relationship between diabetic microvascular complications and stroke present conflicting data. Hence, this study aimed to investigate the effects of diabetic complications on ischemic stroke among individuals with T2DM.

PATIENTS AND METHODS

The records of all patients (n=5,468) who presented to the neurology outpatient clinic of the Afyonkarahisar Health Sciences University Hospital between January 1, 2021, and June 1, 2022, were retrospectively reviewed. Records of 911 patients who were diagnosed with T2DM at least two years ago were separated from the others. Thirty-seven patients who had a history of hemorrhagic cerebrovascular disease were excluded. Consequently, 874 patients (460 males, 414 females; mean age: 65.5±12.1 years; range, 39 to 92 years) with T2DM were included in the study. Demographic characteristics (age and sex), history of chronic disease other than diabetes, duration of diabetes, retinopathy, nephropathy, peripheral arterial disease, and diabetes medications (oral antidiabetics and insulin injection) were recorded. The patients were clustered into two groups: those with and without a history of ischemic stroke. The groups were compared in terms of demographic characteristics and diabetic complications.

Diabetic nephropathy was defined as the concentration of microalbuminuria in spot urine >30 mg/g. Patients using renin-angiotensin system inhibitors due to diabetic nephropathy were also considered patients with diabetic nephropathy. Patients with proliferative or nonproliferative retinopathy in the previous fundus examination were considered patients with retinopathy. If the ankle/brachial index was checked before, values <0.95 were accepted as peripheral arterial disease. Patients using medications for the diagnosis of peripheral arterial disease were also considered patients with peripheral arterial disease.

Statistical analysis

The data analysis was conducted using IBM SPSS version 24.0 software (IBM Corp., Armonk, NY, USA). Categorical variables were presented as percentage and frequency. The normal distribution of the continuous variables was tested using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± standard deviation (SD). The chi-square test and, where appropriate, Fisher exact test were used to compare the categorical variables. Continuous variables were compared between groups by using the independent sample t-test. Logistic regression analysis was used to determine the risk factors for ischemic stroke. Multivariate logistic regression analysis was conducted to determine the parameters that were independent risk factors. All p-values presented were bidirectional, and the level of statistical significance was set at $p<0.05$.

RESULTS

The prevalence of ischemic stroke was 18.6% (n=163). The mean age of patients with ischemic stroke was 67.9±9.9 years, and the mean disease duration was 16.9±8.3 years. Among the patients with ischemic stroke, 132 (81%) had hypertension,

TABLE 1
The comparison of the general characteristics of patients in terms of ischemic stroke status

	Stroke (n=163)			Non-stroke (n=711)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			67.9±9.9			64.9±12.5	0.001
Sex							
Male	82	50.3		378	53.2		0.510
Diabetes mellitus duration (year)			16.9±8.3			10.7±4.9	<0.001
Hypertension	132	81		181	25.5		<0.001
Hyperlipidemia	99	60.7		241	33.9		<0.001
Insulin use	108	66.3		160	22.5		<0.001

SD: Standard deviation.

TABLE 2
The comparison of the diabetic complications in terms of ischemic stroke status

	Stroke (n=163)		Non-stroke (n=711)		
	n	%	n	%	*p*
Retinopathy	68	41.7	158	22.2	<0.001
Nephropathy	45	27.6	91	12.8	<0.001
Peripheral arterial disease	27	16.6	22	3.1	<0.001

TABLE 3
Univariate and multivariate logistic regression analysis for determining risk factors for ischemic stroke

	Univariate			Multivariate		
Parameters	OR	95% CI	*p*	OR	95% CI	*p*
Age	1.021	1.006-1.035	0.005	0.996	0.977-1.015	0.684
Diabetes mellitus duration	1.170	1.135-1.207	<0.001	1.096	1.058-1.135	<0.001
Hypertension	12.486	8.143-19.091	<0.001	6.859	4.155-11.321	<0.001
Hyperlipidemia	3.017	2.125-4.284	<0.001	0.927	0.589-1.458	0.742
Insulin use	6.762	4.674-9.783	<0.001	2.190	1.382-3.470	0.001
Retinopathy	2.505	1.751-3.584	<0.001	1.182	0.762-1.831	0.456
Nephropathy	2.598	1.728-3.907	<0.001	0.898	0.534-1.510	0.685
Peripheral arterial disease	6.218	3.439-11.241	<0.001	3.327	1.613-6.865	0.001

CI: Confidence interval.

99 (60.7%) had hyperlipidemia, and 108 (66.3%) used insulin. Patients with ischemic stroke were determined to be older than the others, had diabetes for a longer period, and had higher rates of hypertension, hyperlipidemia, and insulin use (p=0.001, p<0.001, p<0.001, p<0.001, and p<0.001, respectively). Table 1 shows the general characteristics of patients in terms of ischemic stroke status.

Diabetic retinopathy was detected in 68 (41.7%), nephropathy in 45 (27.6%), and peripheral arterial disease in 27 (16.6%) patients with stroke. Diabetic retinopathy, diabetic nephropathy, and peripheral arterial disease were found to be more frequent among patients with ischemic stroke compared to those without (p<0.001, p<0.001, and p<0.001, respectively). Table 2 shows the comparison of the prevalence of diabetic complications in terms of ischemic stroke status.

Examining the parameters differing between the groups by using logistic regression analysis, diabetes duration, hypertension, insulin use, and peripheral arterial disease were determined to be independent risk factors for ischemic stroke (p<0.001, p<0.001, p=0.001, and p=0.001, respectively). Table 3 shows the results obtained from univariate and multivariate logistic regression analyses aiming to determine the risk factors of ischemic stroke.

DISCUSSION

The present study revealed that T2DM duration, hypertension, insulin use, and peripheral arterial disease were independent risk factors for ischemic stroke. Among diabetic patients, microvascular complications in those with ischemic stroke history were found to be significantly higher compared to diabetic patients with no history of ischemic stroke. Retinopathy was found in 41.7% of those who had an ischemic stroke, nephropathy in 27.6%, and peripheral arterial disease in 16.6%.

In this study, diabetic nephropathy and diabetic retinopathy were considered potential risk factors for ischemic stroke in univariate analyses, whereas multivariate analyses revealed that these two diabetic microvascular complications were not independent risk factors for ischemic stroke.

In a study conducted on stroke epidemiology in Türkiye, it was observed that the frequency of stroke increased with the aging population.[14] Acute stroke is a significant public health issue, and the management of acute stroke should be improved; however, stroke prevention is of even greater priority. Therefore, it is important to identify and manage risk factors associated with stroke.

Diabetes mellitus has been identified as an independent risk factor for stroke.[7] Additionally, it was noted in a previous study that the risk of stroke escalates with the duration of diabetes.[15] In the current study, the duration of diabetes was recognized as an independent risk factor for stroke.

Hypertension was noted to be one of the most common and significant risk factors for the development of ischemic stroke.[16] Furthermore, it was reported that high blood pressure after a stroke reduces the likelihood of neurological recovery, and hypertension was associated with neurological deterioration and poor functional outcomes.[17] In the present study, hypertension was found to be very high among stroke patients, and a significant correlation was found between hypertension and stroke.

Several studies have emphasized the increased incidence of cardiovascular diseases associated with insulin use. These studies suggest that intensive insulin therapy may elevate the risk of hypoglycemia, which in turn could be linked to cardiovascular events.[18-22] In the present study, we observed a higher incidence of ischemic stroke in patients using insulin. This association may contribute to the risk of ischemic stroke through mechanisms related to cardiovascular pathophysiology. Therefore, larger-scale studies that examine patients with both cardiovascular and ischemic conditions are warranted to further explore this connection.

Peripheral arterial disease and stroke are the main clinical manifestations of atherothrombosis. Recent reports indicated a high prevalence of peripheral arterial disease among acute ischemic stroke patients, with prevalence estimates ranging between 31 and 51%. These mechanisms include atherothrombosis, inflammation, endothelial dysfunction, platelet activation, and hypercoagulability.[23,24] The results achieved in the present study align with the significant relationship between stroke and peripheral arterial disease.

In a cohort study involving 50,180 patients with atrial fibrillation, diabetic retinopathy was detected in 2.6% of participants and diabetic nephropathy in 8.4%.[13] In another study including 1,253 patients diagnosed with T2DM, the prevalences of macrovascular complications were determined to be 30.5% for coronary artery disease, 10.1% for stroke, and 12.0% for diabetic foot.[25] In the same study, among microvascular complications, nephropathy was observed in 34.2%, retinopathy in 25.1%, and neuropathy in 5.8%. In a different study involving newly diagnosed prediabetic individuals, microvascular complications were observed in 12% of participants (neuropathy in 4% and nephropathy in 8%).[26] The same study also revealed that 19% of individuals had macrovascular complications.

A meta-analysis investigating the correlation between diabetic retinopathy and stroke in individuals with T2DM revealed an elevated risk of stroke associated with diabetic retinopathy.[8] This increased risk may be attributed to the close connection between retinal and cerebral microvessels and the shared risk factors for both diabetic retinopathy and stroke, such as elevated hemoglobin A1c, hyperglycemia, hypertension, and dyslipidemia. The association between diabetic retinopathy and stroke in patients with type 1 diabetes mellitus remains uncertain.[8] Similarly, another meta-analysis established a link between diabetic retinopathy and stroke in patients with T2DM, while the relationship in patients with T1DM remained unclear.[9]

Cerebral microvascular structures play an important role in regulating many brain processes, and dysfunction in these structures might increase susceptibility to conditions such as lacunar and hemorrhagic stroke, cognitive impairment, and depression. The primary triggers of cerebral microvascular dysfunction associated with diabetes include hyperglycemia, obesity, insulin resistance, and hypertension.[27]

Studies carried out in Japan, China, and the USA reported an increased risk of ischemic stroke in patients with diabetic nephropathy.[10-12] In a large-scale study involving a diverse population of adult patients with T2DM, increased albuminuria and worsening of diabetic nephropathy were independently associated with a higher risk of stroke compared to those without diabetic nephropathy.[28] A cohort study investigating the risk of ischemic stroke in diabetic patients with atrial fibrillation with and without microvascular complications found

through multiple analyses considering all risk factors that the risk of ischemic stroke was similar in patients without complications.[13]

In the present study, as in other studies, singular analyses revealed that retinopathy and nephropathy increased the risk of ischemic stroke. However, in multiple analyses examining microvascular complications together with other etiological factors, no significant role was observed for microvascular complications. Nevertheless, there is a lack of sufficient studies addressing this subject, and further studies considering all factors in stroke etiology are needed to evaluate the relationship between diabetic microvascular complications and ischemic stroke.

Limitations of the study include the single-center, retrospective design, the small number of study groups, and selection bias. Other limitations include not evaluating other potential risk factors for stroke and not examining neuropathy among microvascular complications.

In conclusion, duration of diabetes, insulin use, hypertension, and peripheral arterial disease were found to be independent risk factors for ischemic cerebrovascular events. Retinopathy and nephropathy, which are microvascular complications of diabetes, were not independent risk factors for ischemic cardiovascular events. The results achieved in this study hold significant implications for clinical management and preventive strategies. A broader perspective on the assessment of the risk of ischemic stroke in individuals with diabetes provides valuable insights for disease management and prevention. Understanding the risk of ischemic stroke in individuals with diabetes is of critical importance for disease management and public health. It is anticipated that future large-scale studies will contribute to a deeper understanding of this intricate relationship.

Ethics Committee Approval: The study protocol was approved by the Afyonkarahisar University of Health Sciences Clinical Research Ethics Committee (date: 07.10.2022, no: 2022/467). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: Patient data collection has been conducted retrospectively from records registered in the hospital. Therefore, informed consent has not been obtained through voluntary participation.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Study design, data analysis, interpretation of results, writing and revising the manuscript: G.Z.D.; Data collection, literature review, interpretation of results, writing and revising the manuscript: S.B.A.

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