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ORIGINAL ARTICLE

White matter cerebral lesions in patients with migraine and its relationship with the triglyceride-glucose index

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ABSTRACT

Objectives: The study aimed to investigate the relationship between the triglyceride-glucose (TyG) index and white matter changes in patients with migraine.

Patients and methods: In this prospective case-control study, brain magnetic resonance imaging, fasting triglyceride levels, and fasting glucose levels of 80 patients (69 females, 11 males; mean age: 31.7±9.8 years; range, 19 to 57 years) with migraine and 50 controls (39 females, 11 males; mean age: 29.6±8.6 years; range, 18 to 50 years) were evaluated between January 2023 and January 2024. Headache intensity, frequency, and characteristics were recorded. Headache disability was measured using the MIDAS (Migraine Disability Assessment). White matter hyperintensities (WMHs) were assessed with the Fazekas scale. The TyG index was calculated with the following formula: fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2.

Results: Based on the Fazekas score for white matter hyperintensities (WMHs), the TyG index was significantly higher in patients with Stage 1 and Stage 2 compared to those with Stage 0 (p=0.038).

Conclusion: The findings suggested that an elevated TyG index was associated with the development of WMHs in patients with migraine.

Keywords: Migraine, triglyceride-glucose index, white matter lesion.

Migraine is a disorder characterized by recurrent headache attacks that are moderate to severe in intensity, often unilateral and pulsating in nature, aggravated by routine physical activity, and associated with nausea, photophobia, or phonophobia. Due to its high prevalence, migraine creates a significant socioeconomic burden and profoundly affects quality of life.[1] Owing to advances in neuroimaging, migraine is now known not as a merely vascular condition, but as a neurovascular disorder of the central nervous system.[2] Cerebral small vessel disease (CSVD) represents a cluster of pathologies of heterogeneous etiology with potential implications for the cerebrovascular system, including small arteries, capillaries, and small vessels. Typical lesions resulting from CSVD are characterized by white matter hyperintensities (WMHs), lacunes, microbleeds, enlarged perivascular spaces (EPVS), and microinfarcts.[3] In patients with migraine, WMHs are detected via brain magnetic resonance imaging (MRI).[4] White matter hyperintensities are reported to be equally prevalent in migraine with aura and chronic migraine.[5]

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The triglyceride-glucose (TyG) index serves as an indicator of insulin resistance (IR) and is associated with various metabolic syndromes and cardiovascular and cerebrovascular conditions.[6] The literature points out a statistically significant correlation between an elevated TyG index value and the occurrence of both macrovascular and microvascular diseases. The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) is the tool employed by most studies focusing on the relationship between IR and CSVD. An association was reported between HOMA-IR results and the total CSVD score, silent cerebral infarcts, WMHs, and EPVS. However, most of the studies in this area were conducted in relatively healthy populations and did not exclude diabetic patients.

A recent cross-sectional study suggested that the TyG index exhibited a slightly stronger correlation with the prevalence of silent brain infarctions and WMH volume than the HOMA-IR assessment result.[3] Nevertheless, in the literature, the relationship between the TyG index and WMHs in patients with migraine has not been investigated. This study is the first to investigate this association. Consequently, this study aimed to explore whether the TyG index in nondiabetic patients with migraine was correlated with white matter alterations irrespective of other clinical risk factors.

PATIENTS AND METHODS

The prospective case-control study was conducted with 80 patients (69 females, 11 males; mean age: 31.7±9.8 years; range, 19 to 57 years) who were admitted to the neurology outpatient clinic of the Dr. Ersin Arslan Training and Research Hospital, between January 2023 and January 2024 and were subsequently diagnosed with migraine. The patients included in the study underwent brain MRI and were checked for their fasting triglycerides and fasting glucose values for various reasons in the last year. The following formula was used to determine the TyG index: fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2 log scale. Additionally, the study included 50 controls (39 females, 11 males; mean age: 29.6±8.6 years; range, 18 to 50 years) who underwent brain MRI and had their fasting triglycerides and fasting glucose levels checked within the past year at the same hospital. All patients with migraine included in the study met the migraine criteria defined by the International Headache Society. The study sample excluded patients with hypertension, diabetes, cardiovascular disease, renal disease, endocrine/metabolic disorders, or central nervous system vasculitis, history of stroke, smoking/alcohol/substance use, malignancy, and those with a body mass index greater than 30. The authors recorded the demographic data of the subjects, including personal and family history and daily habits, before moving on to conduct a headache investigation questionnaire among the cases. The study protocol was approved by the Gaziantep University Clinical Research Ethics Committee (date: 09.11.2022, no: 2022/347). Written informed consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients were questioned about their migraine disease duration. The symptoms accompanying headache (nausea, vomiting, photophobia, visual disturbances, and hypoesthesia-hemiparesis) were identified.

The Migraine Disability Assessment (MIDAS) is a tool designed to assess the level of disability experienced by patients with migraine in their work, home, and social life. In this study, the patients were asked targeted questions relating to their experience in the last three months. Each question inquired about the number of days they were affected by headaches in their work, home, and social life. As a result, every patient's total disability score was calculated, with 1 point added for each of such days. The total scores were then employed to divide the cases into four groups (0-5 days= little or no disability; 6-10 days= mild disability; 11-20 days= moderate disability; ≥21 days= severe disability). In addition, the number of headache attacks in the last three months was recorded. The patients were asked to rate their headache intensity on a scale from 0 (no pain) to 10 (worst possible pain). The patients were then divided into distinct groups according to their responses (5-6= moderate; 7-8= severe; 9-10= unbearable pain).[7,8]

The study considered the MRI scans in the last six months. The scans were evaluated and assessed using Magnetom Avanto 1.5 T (Siemens Healthcare, Erlangen, Germany). The parameters applied for the MRI evaluation were 230 mm for the field of vision, 256×256 for the matrix, 5 mm for thickness, 1 mm for the gap, 2 to 3 for the number of excitations, and 15/500 msec for echo and repetition time. The Fazekas scale was

employed for the identification and categorization of white matter lesions. Based on the the results on this scale, patients were categorized into four groups (no lesions or a single lesion= Fazekas 0; multiple punctate lesions= Fazekas 1; beginning confluence of lesions= Fazekas 2; large confluent areas= Fazekas 3). The patients were further divided into two groups for examination in line with the presence or absence of WMHs.[9]

Statistical analysis

The data were analyzed using IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). The numerical data were analyzed with the help of mean ± standard deviation (SD) and median (min-max) values. Category-specific data were summarized in frequency (n) and percentage (%), and comparisons were conducted with the chi-square test or Fisher exact test. Data distribution was assessed via the Kolmogorov-Smirnov and Shapiro-Wilk tests. Student's t-test and the Mann-Whitney U test were employed for the analysis of numerical data (in line with data distribution). Spearman's correlation test was used to evaluate the relationship between numerical variables. In terms of correlation coefficients, 0-0.25 indicated a weak correlation, 0.25-0.50 a weak to moderate correlation, 0.50-0.75 a strong correlation, and 0.75-1.00 a very strong correlation. A p-value <0.05 was considered statistically significant.

RESULTS

The median time since diagnosis was 5.2±5.0 years among the patients. The effects of migraine on daily activities were evaluated on the MIDAS, and the scores from the study sample indicated that 10 (12.5%) patients had Grade 1, 10 (12.5%) had Grade 2, 11 (13.8%) had Grade 3, and 49 (61.3%) had Grade 4 disability scores.

An evaluation of the blood lipid profile and TyG index in the case and control groups indicated that low-density lipoprotein (LDL) and total cholesterol levels were higher in patients with migraine (p=0.007 and p=0.034, respectively). The blood lipids, glucose, and TyG index values of patients with migraine and the subjects in the control group are summarized in Table 1.

An examination was undertaken to identify the associations, if any, between the pain character (pain duration, pain localization, pain type, accompanying symptoms, and presence or absence of aura) and blood parameters, and no statistically significant difference was found in blood lipids, glucose, and TyG index values (p>0.05). The blood parameters were also considered in the context of MIDAS scores, and the LDL cholesterol level was established to be higher in patients with Grade 3 disability than in the remaining groups (p=0.031). No statistically significant differences were observed among other sets of data. The groups were then reorganized into two groups, with Grades 1 and 2 indicating mild and Grades 3 and 4 indicating moderate to severe disability. Under this new categorization, the levels of high-density lipoprotein, LDL, and total cholesterol, triglycerides, glucose, and the TyG index were found to be similar between the groups. No statistically significant differences were detected among the groups (p=0.403, p=0.059, p=0.228, p=0.798, p=0.073, and p=0.894, respectively). The comparison of blood lipids, glucose, and the TyG index values according to MIDAS scores is summarized in Table 2.

An examination of the blood parameters of patients according to their Fazekas scores revealed that triglycerides, LDL, and total cholesterol levels were higher in Fazekas Grades 1 and 2 compared to Grade 0. However, a statistically significant rise was observed only in the level of triglycerides (p=0.019). Similarly, the TyG index was significantly higher in Stages 1 and 2 compared to Stage 0 (p=0.038). Blood glucose levels were similar across all groups (p=0.637). The comparison of blood lipids, glucose, and the TyG index values according to Fazekas scores is summarized in Table 3.

The correlation analysis results related to MIDAS scores indicated a positive correlation between blood LDL levels and pain duration in

TABLE 1
Blood lipids, glucose, and TyG index values in patient and control groups

	Patient group	Control group	
	Mean±SD	Mean±SD	*p*
HDL cholesterol	49.91±9.06	50.20±13.70	0.587
LDL cholesterol	112.75±26.77	98.41±31.21	0.007*
Total cholesterol	183.71±35.66	171.16±37.15	0.034*
Triglycerides	106.68±57.48	102.68±46.62	0.998
Glucose	88.02±8.26	87.58±8.34	0.678
TyG index	4.72±2.68	4.52±2.21	0.904

TyG: Triglyceride-glucose; SD: Standard deviation; HDL: High-density lipoprotein; * Statistical significance parameter.

TABLE 2
Blood lipids, glucose, and TyG index values according to MIDAS scores

	Grade 1 (n=10)	Grade 2 (n=10)	Grade 3 (n=11)	Grade 4 (n=49)	
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	*p*
HDL cholesterol	48.37±9.65	53.14±6.51	55.14±14.20	48.18±7.50	0.209
LDL cholesterol	105.37±21.50	98.57±28.41	138.57±21.85	111.92±25.52	0.031*
Total cholesterol	177.12±33.61	171.71±26.76	215.57±32.40	180.51±36.06	0.091
Triglycerides	108.80±53.69	95.20±63.28	114.90±49.69	106.75±59.90	0.565
Glucose	89.70±8.26	92.60±5.01	87.63±7.48	86.83±8.75	0.260
TyG index	4.94±2.70	4.38±2.92	5.08±2.39	4.66±2.75	0.795

TyG: Triglyceride-glucose; MIDAS: Migraine Disability Assessment; SD: Standard deviation; HDL: High-density lipoprotein; * Statistical significance parameter.

TABLE 3
Blood lipids, glucose, and TyG index values according to Fazekas scores

	Stage 0 (n=38)	Stage 1 (n=31)	Stage 2 (n=11)	
	Mean±SD	Mean±SD	Mean±SD	*p*
HDL cholesterol	50.17±8.35	51.30±9.32	44.33±10.28	0.162
LDL cholesterol	104.78±26.43	119.30±23.82	121.50±33.11	0.086
Total cholesterol	171.20±34.58	195.78±27.93	195.50±49.28	0.053
Triglycerides	85.28±31.72	123.83±69.78	132.27±66.32	0.019*
Glucose	88.21±9.74	88.06±7.13	87.27±5.86	0.637
TyG index	3.74±1.40	5.52±3.30	5.84±3.11	0.038*

TyG: Triglyceride-glucose; SD: Standard deviation; HDL: High-density lipoprotein; * Statistical significance parameter.

years (p=0.027, r=0.317). A negative correlation was observed between blood glucose levels and MIDAS items 3 and 4 and MIDAS A (p=0.045, r=–0.224; p=0.025, r=–0.251; p=0.025, r=–0.251, respectively). However, no strong correlations were identified among these parameters. The correlation analysis of blood lipids, glucose, and TyG index values according to MIDAS scores is summarized in Table 4.

DISCUSSION

Migraine, the third most common medical condition worldwide, is a well-known independent risk factor for subclinical focal deep white matter lesions, even in young and healthy individuals without any cardiovascular risk factors. Despite the prevalence of migraine-associated deep WMHs, their pathophysiology is yet to be fully understood.[10] The occurrence of WMHs may be attributed to brain damage linked to metalloproteinases activated during cortical spreading depolarization, ischemic microvascular disorders associated with regional hypoperfusion, microemboli, hypercoagulability, and endothelial dysfunction. Oxidative stress is present in both ictal and interictal phases in migraine, which may explain the occurrence of WMHs in patients with migraine.[11] The detection rate of WMHs in the MRI scans of patients with migraine ranges from 30 to 43%.[12,13] Studies indicate that while some patients with migraine exhibit WMHs in their MRI, others do not. Furthermore, patients with WMHs identified in their MRI exhibit a variation in terms of the intensity of such hyperintensities. It is clear that migraine is a risk factor for the development of WMHs. However, uncertainty still prevails as to the causes of the presence or absence of WMHs in patients with migraine and the variability of intensity in patients with WMHs.

The HOMA-IR is the indicator employed by most studies focusing on the relationship between IR and CSVD. The HOMA-IR result was found to be associated with the total CSVD score, silent cerebral infarcts, WMHs, and EPVS.

TABLE 4
Correlation of blood lipids, glucose, and TyG index values according to MIDAS scores in patients with migraine

	HDL cholesterol	LDL cholesterol	Total cholesterol	Triglycerides	Glucose	TyG index
Pain duration in years						
p	0.945	0.027*	0.089	0.208	0.494	0.368
r	0.010	0.317	0.245	0.142	0.078	0.102
MIDAS Item 1						
p	0.318	0.176	0.316	0.261	0.757	0.316
r	0.146	0.196	0.146	0.127	0.035	0.114
MIDAS Item 2						
p	0.260	0.771	0.966	0.406	0.197	0.325
r	0.164	0.043	0.006	0.094	-0.146	0.111
MIDAS Item 3						
p	0.191	0.889	0.948	0.996	0.045*	0.683
r	0.191	0.020	0.010	0.001	−0.224	0.046
MIDAS Item 4						
p	0.304	0.385	0.620	0.586	0.021*	0.278
r	−0.150	0.127	0.073	−0.062	−0.257	0.123
MIDAS Item 5						
p	0.334	0.356	0.589	0.476	0.218	0.304
r	0.141	0.135	0.079	0.081	0.139	0.116
MIDAS A						
p	0.079	0.829	0.807	0.908	0.025*	0.821
r	0.253	0.032	0.036	0.013	−0.251	0.026
MIDAS B						
p	0.292	0.356	0.391	0.661	0.092	0.966
r	0.154	0.135	0.125	0.050	0.190	0.005
MIDAS total						
p	0.266	0.336	0.563	0.494	0.074	0.293
r	0.162	0.140	0.085	0.078	0.201	0.119

TyG: Triglyceride-glucose; MIDAS: Migraine Disability Assessment; HDL: High-density lipoprotein.

However, the majority of the relevant studies were conducted with relatively healthy populations and did not exclude patients with diabetes. A recent cross-sectional study suggested that the TyG index exhibited a slightly stronger correlation with the prevalence of silent brain infarctions and WMH volume than the HOMA-IR assessment results.[3] The literature search undertaken for this study failed to reveal any similar study investigating the association between WMHs in migraine and the TyG index. The present study stands out with this unique investigation. Additionally, the study was conducted with a sample that excluded patients with diabetes, individuals aged 45 and older, and individuals with a body mass index of 30 or higher. In this study, we found a significant correlation between the TyG index and the occurrence of WMHs in patients with migraine.

The TyG index, a simple and widely accessible measure, has recently emerged as a new biomarker for cardiovascular and metabolic disorders. A higher TyG index indicates a higher likelihood of hyperglycemic and dyslipidemic conditions that may lead to cerebro-cardiovascular atherosclerosis. Previous studies reported that a high TyG index was predictive of arterial stiffness, coronary artery calcification, functional kidney dysfunction, and ischemic cardiovascular events. Additionally, a high TyG index may precede metabolic syndrome and type 2 diabetes and predict these conditions at the onset. In this context, a higher TyG

index may be a risk factor for the development of cerebrovascular microangiopathy; however, more data are needed to clarify this potential correlation. The exact mechanism of a higher TyG index contributing to the development of WMHs in the brain is not fully explained, but it is possible to employ certain possible explanations to identify the assumed mechanisms.

First, endothelial dysfunction, a crucial step in the progression of small vessel disease, may play a significant role in the pathophysiology of WMHs. Previous studies reported evidence of endothelial dysfunction in individuals with ischemic cerebral microangiopathy and WMHs. Fluid leakage from cerebral circulation and subsequent endothelial damage lead to structural changes in perivascular spaces, causing white matter lesions.

Second, low-grade inflammation may contribute to the correlation between the TyG index and WMHs. Many studies indicate that reactive oxidative stress and low-grade inflammation play significant roles in the pathophysiology of endothelial dysfunction. Previous studies suggested a close connection between proinflammatory cytokines and ischemic cerebral microangiopathy and WMHs.[6,14,15]

The association between WMHs and the clinical characteristics of migraine is still unclear. While some studies suggested that WMHs were more common in migraine patients who experience more frequent headache attacks or exhibit longer disease durations, others reported no association between WMHs and disease duration or attack frequency.[13,16-18] In the present study, no association was found between disease duration and attack frequency and the Fazekas scores determined according to WMH intensity. Some studies supported that the prevalence of WMHs in individuals with migraine with aura was significantly higher than those without aura, while others failed to offer support for this association.[12,13,19,20] In the present study, no significant association was found between the Fazekas score determined according to WMH intensity and migraine subtype (with or without aura). White matter hyperintensities are also common in the general population and may be attributed to the normal ageing process. Ageing contributes independently to the prevalence of WMHs.[11,21] The present study only included subjects under 45 years of age to avoid any bias with respect to the prevalence of WMHs in patients of advanced age. The present study did not establish any association between the clinical characteristics of migraine and the occurrence of WMHs.

This study had a few limitations. First, it was a single-center study with a relatively small sample size. Additionally, the association between the location of WMHs and the TyG index was not analyzed. As a result, a higher TyG index may be associated with a higher prevalence of WMHs in patients with migraine under 45 years of age, irrespective of other clinical risk factors.

In conclusion, the findings suggested that the TyG index was an independent risk factor for the development of WMH in patients with migraine.

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

Author Contributions: Writing, original draft: A.T.Y.; Data collection: Ş.Ç.G, A.T.Y.; Revising the manuscript/study supervision: A.T.Y., R.Ş, G.Ö, Ş.Ç.G, F.E, B.S.S.U.

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