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Atherogenic plasma index is associated with ischemic cerebrovascular events due to carotid artery disease

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ABSTRACT

Aims: Low molecular weight lipoprotein (LDL) and triglyceride (Tg), among cardiovascular disease risk factors, are replaced by markers with higher sensitivity and specificity. The atherogenic plasma index (API) has a strong predictive power for cardiovascular diseases. In our study, we aimed to compare the predictive power of API and other lipid parameters in detecting carotid artery disease (CAS) in patients with ischemic stroke.

Methods: A total of 878 individuals were analyzed, and 583 patients with ischemic stroke were enrolled in this study. The patients were divided into two groups according to the presence or absence of carotid artery disease in the Doppler ultrasound examination. Demographic data and lipid parameters were compared between both groups.

Results: The mean age of the patients with CAS was statistically significantly higher than the other group (74.33±11.27 vs 70.11±13.57; p=0.002). The Tg/HDL ratio was higher in patients with CAS than those without (3.80±2.83 vs 3.69±2.57; p=0.048). API was found to be statistically significantly higher in the group of patients with CAS compared to the other group (0.67±0.32 vs 0.48±0.25; p=0.024). Tg/HDL ratio and API were determined as predictive parameters for CAS in patients with ischemic cerebrovascular stroke. [OR: 1.345 (0.712-1.437); p=0.048, OR: 7.21 (0.881-8.056); p=0.023].

Conclusion: Conflicting results regarding the relation between atherosclerosis and conventional lipid parameters led to more specific subgroups being investigated. API shows a good correlation with the highly sensitive LDL subfraction in terms of atherosclerosis. API is a feasible variable predicting the presence of CAS in patients with ischemic stroke.

Keywords: Low-density lipoproteins, small dense low-density lipoproteins, atherogenic plasma indexes, carotid artery disease

INTRODUCTION

Ischemic stroke is the second most common cardiovascular disease, leading to mortality and morbidity.[1] Carotid atherosclerosis is the main cause of ischemic stroke. It occurs when the atherosclerotic plaque rupture is complicated by intra-plaque bleeding, superficial ulceration, and thrombus formation.[2]

The first step in the development of ischemic stroke is the formation of atherosclerosis. Risk factors for atherosclerosis increase the risk of stroke. Lipid parameters are one of the leading factors among these factors. Low-density lipoproteins (LDL) cause increased risk, while high-density lipoproteins (HDL) have a protective effect. Given the structural differences between lipoprotein subgroups and apolipoproteins with different densities, it remains unclear which subgroups Show a more reliable correlation between stroke and lipids.[3] Resolving the link between atherogenic lipoproteins and stroke has clinical importance in terms of protection from cerebrovascular diseases. Clarifying the relationship between atherogenic lipids and the pathogenesis of stroke is important for the reconstruction of preventive treatment approaches. Extensive randomized studies have shown that the use of statins reduces the risk of ischemic stroke.[4] On the other hand, the view of managing all atherosclerotic processes with LDL cholesterol alone is getting weaker. The idea of a complete evaluation of high triglyceride (Tg), HDL, and LDL has led to the development of an atherogenic plasma index (API). API was defined by Dobiasova et al.[5] as the logarithm of Tg to HDL in base 10. Since its definition, it has been closely correlated with atherosclerosis and cardiovascular diseases.[6,7] Atherogenic lipoproteins are characterized by an increase in the concentration of small-density LDL and large VLDL and a decrease in HDL concentration. This profile is an indicator of high risk for coronary and carotid artery diseases. API defines the atherogenic index of plasma, reflecting lipid subgroups. High API value has been associated with cardio-metabolic events.[8]

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In our study, we hypothesized that API might have a determining role in carotid atherosclerosis in patients with ischemic stroke. Our study aims to investigate the effect of lipid subgroups in predicting carotid artery disease/stenosis (CAS) in the etiology of stroke in patients with ischemic stroke.

METHODS

The study was initiated with the approval of the Siirt University Medical Faculty Clinical Researches Ethics Committee (Date: 13.12.2022, Decision No: 62448). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. A total of 878 patients admitted to our center with a cerebrovascular event and hospitalized between 2018 and 2022 were retrospectively analyzed through computer system records. Among these patients, 610 patients were included in the study. Twenty-seven patients were excluded from the study due to the inadequacy of the system records, death during the examinations, and simultaneous hemorrhage.

The study encompassed 583 patients who were diagnosed with ischemic cerebrovascular stroke. These patients were bifurcated into two groups: those who had carotid artery stenosis and those who did not. The system was used to gather demographic characteristics and laboratory data of the patients. The recorded information included age, gender, hypertension (HT), atrial fibrillation (AF), Diabetes mellitus (DM), obesity, peripheral artery disease, heart failure (ejection fraction <45%), peripheral artery disease, coronary artery disease, smoking, and laboratory parameters.

To minimize the effect of cirCASian rhythm on blood tests, blood samples were taken early in the morning after at least 10 hours of fasting. Total cholesterol, TG, and HDL concentrations were measured in the biochemistry laboratory using enzymatic methods. LDL was calculated according to the Friedewald formula.

All biochemical analyses were done with fresh blood samples. AIP was found by calculating the base ten logarithmic transformations of the ratio of TG to HDL (TG/HDL) in accordance with the formula defined by Dobiasova et al.[5]

Doppler ultrasound was used to diagnose CAS. Doppler ultrasonography measurements were taken from the distal segment of the common carotid artery on both sides, with carotid B-mode Doppler ultrasound performed by two experienced radiologists. Intima-media thickness (IMT) is one of the parameters used to determine atherosclerosis. The distal 1 cm part of the common carotid artery, internal carotid artery, and bifurcation were scanned with 2D Doppler. The radiologist who took the imaging obtained different sections using anterior, posterior, and lateral angles.[9] Among these sections, the thickest IMT distance was selected. The atherosclerotic plaque was defined as a focal thickening with a minimum thickness of at least 1.3 mm, at least 50% greater than the surrounding vessel wall. It showed a reliability coefficient of 0.85 for the common carotid artery. The differences between radiologists were evaluated by using Pearson's correlation coefficients. The difference for each operator was less than 0.05.

Statistical Analysis

Statistical analysis was conducted using the SPSS 22.0 software package from IBM Corp. Continuous variables were expressed as mean±standard deviation, and percentages were used for categorical variables. Non-normally distributed variables were presented as median (minimum-maximum) values. The distribution characteristics of variables were determined using the Kolmogorov-Smirnov and Shapiro-Wilks tests. Changes observed in non-normally distributed variables were analyzed using the Friedman test. The differences between continuous variables were assessed using a paired sample t-test. The Spearman correlation coefficient was used to examine the correlation of the analysis. A probability (p) value of less than 0.05 was considered statistically significant.

RESULTS

Among the 878 patients who were admitted to the hospital with a cerebrovascular accident, 583 patients were included in the study among the patients who had an ischemic stroke. The mean age of the patients with CAS was statistically significantly higher than the other group (74.33±11.27 vs 70.11±13.57; p=0.002). Gender and rates of chronic diseases other than atrial fibrillation (AF) were similar. AF was more common in the patient group without CAS (29.4% vs 36.1%; p=0.006). The incidence of coronary artery disease was significantly higher in the patient group with CAS (24.7% vs 16.3%; p=0.039). No statistically significant difference was observed between hemogram and biochemistry parameters. Although LDL and T-COL levels were higher in the CAS group, the difference was not statistically significant. The Tg/HDL ratio was found to be higher in patients with CAS than those without (3.80±2.83 vs 3.69±2.57; p=0.048). API was found to be statistically significantly higher in the group of patients with CAS compared to the other group (0.67±0.32 vs 0.48±0.25; p=0.024). Other and all results are shown in Table 1.

Tg/HDL, API, LDL/HDL, and MON/HDL parameters were evaluated with binary logistic regression analysis

Table 1. Comparison of demography, hemogram and lipid parameters in the population of ischemic stroke patients with and without carotid artery disease

Variables	CAS (442)	NO (141)	P value
Age	74.33±11.27	70.11±13.57	0.002
Male sex	50.7% (n:224)	48.2% (n:68)	0.612
Hypertension	40.0 (n:177)	36.9 (n:52)	0.503
Diabetes mellitus	29.9 (n:132)	26.2 (n:37)	0.409
AF	29.4 (130)	36.1 (51)	0.006
Morbid obesity	3.2 (14)	5.7 (8)	0.174
PAD	6.6 (29)	4.3 (6)	0.316
HF	15 (66)	8.5 (12)	0.054
CAD	24.7 (109)	16.3 (23)	0.039
Smoking	10.9 (48)	7.1 (10)	0.193
Hgb	13.66±1.82	13.51±2.07	0.487
WBC	9.28±2.93	9.19±4.10	0.815
PLT	241.08±78.94	248.94±78.93	0.324
RDW	50.87±8.74	50.55±11.12	0.768
NEU	6.24±3.04	6.30±3.60	0.879
LYMP	2.25±1.02	2.07±1.14	0.099
MON	0.54±0.25	1.12±1.78	0.615
T-COL	184.83±51.39	178.02±44.71	0.145
TG	147.18±78.65	142.98±77.84	0.594
HDL- C	43.52±12.30	44.24±12.31	0.418
LDL- C	116.46±40.69	111.25±37.22	0.175
TG/HDL	3.80±2.83	3.69±2.57	0.048
API	0.67±0.32	0.48±0.25	0.024
LDL/HDL	2.85±1.24	2.75±1.21	0.422
MON/HDL	0.013±0.08	0.032±0.40	0.211

Abbreviations: CAS: Carotid artery disease, CAD: Coronary artery disease, AF: Atrial fibrillation, PAD: Peripheral artery disease, HF: Heart failure, Hgb: Hemoglobin, WBC: White blood cell count, PLT: Platelet count, RDW: Red cell distribution width, NEU: Neutrophil count, LYMP: Lymphocyte count, MON: Monocyte count, T-COL: Total cholesterol, TG: Triglycerides, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, API: Atherogenic plasma index

to determine the lipid parameters predicting CAS in patients with ischemic stroke. Tg/HDL ratio and API were determined as predictive parameters for CAS in patients with ischemic cerebrovascular stroke [OR: 1.345 (0.712-1.437); p=0.048, OR: 7.21 (0.881-8.056); p=0.023] (Table 2).

Table 2. Binary logistic regression–lipid parameters independently associated with ischemic SVO due to carotid artery disease

Variable	P value	Exp (B)	OR 95% CI
Tg/HDL	0.048	1.345	0.712–1.437
API	0.023	7.21	0.881–8.056
LDL/HDL	0.732	1.033	0.859–1.241
MON/HDL	0.820	0.545	0.070–4.929

Nagelkerke R square=0.504, Cox&Snell R square=0.337

DISCUSSION

Cardiovascular diseases continue to be the most important cause of morbidity and mortality despite all the advancements in the medical treatment field. It is known that some of the events that occur are preventable with appropriate treatment goals. Ischemic stroke, which has a significant share in cardiovascular diseases, has been the subject of many studies in terms of etiology. Different lipid parameters and mathematical combinations of lipid subgroups have been reported as predictive variables. Despite extensive studies, there is no consensus on a lipid subgroup. In our study, we investigated the CAS predictive powers of lipids in patients with ischemic stroke. The motivation of this study was the hypothesis that API is indicative of the atherogenic dyslipidemia profile.

Lipid parameters that predict CAS in the etiology of ischemic stroke were evaluated in this study. Among the lipid parameters, API was observed as a statistically significant variable for predicting CAS in patients with ischemic stroke.

Plaque formation on the carotid artery is one of the most important predictors of ischemic stroke. Doppler ultrasound, which has an important role in determining the plaque, also gives information about the morphology of the plaque. It is known that echolucent plaques cause complicated ischemic stroke more frequently. Echogenic plaques contain more fibrous tissue and tend to calcify. This makes the plate more stable. Echolucent plaques are rich in lipids. Population-based studies have reported that people with echolucent plaques have lower HDL cholesterol levels.[10] In literature conducted from the past to the present, significant correlations have been established between the development of atherosclerosis and different lipid parameters in the etiology of CAS.

Current evidence is that LDL, Tg, and apoB molecules increase the risk of stroke. Circulating lipoproteins contain varying degrees of cholesterol and Tg. This leads to uncertainty in the measurement of the level of atherogenic lipoproteins.[11] According to the Mendelian randomization study, which consisted of MEGASTOKE data from 514,791 participants, univariant analyses showed that high Tg, LDL, apoB, and low HDL levels cause an increased risk of ischemic stroke. However, multivariate analyses reported that the potency of Tg and LDL decreased relative to apoB and even attenuated to null after mutual adjustment.[3] In a study of 402 patients examining the correlation between serum lipids and carotid plaque formation in the Chinese patient population, a significant correlation was observed between the LDL/HDL ratio and the increase in carotid intima-media thickness.[12]

The effects of LDL and HDL levels on early carotid atherosclerosis were investigated in a series of 825 patients by Tamada et al.[13] There was no statistically significant correlation between LDL cholesterol and carotid plaque score in multivariate analyses. However, LDL/HDL ratio was significantly associated with increased carotid plaque scores in both genders. A cross-sectional study conducted with 10,900 patients reported that TC/HDL, Tg/HDL, and LDL/HDL ratios were positively correlated with peripheral arterial diseases. Despite the high number of patients in the study, using only the ankle-brachial index for diagnosing peripheral artery disease created a limitation in the study.[14] On the other hand, in a cross-sectional study of 302 patients by Nimkuntod et al.[15], the LDL/HDL ratio for carotid plaque formation was not found to be statistically significant. In the same study, the presence of carotid plaque was observed in correlation with age, gender, and Tg levels. In a cross-sectional designed MRI study involving 6143 individuals, 24% (n: 1456) of patients had small vessel disease. Hypercholesterolemia was observed to be associated with a decreased small vessel disease risk rate after other risk factors such as age and hypertension were adjusted.[16]

Heretofore, many predictive parameters have been studied to identify individuals at high cardiovascular risk. Ideal parameters for risk analysis should be low-cost, fast, specific, and non-invasive. According to the prospective study of Framingham offspring data, sdLDL demonstrated a strong association with atherosclerotic cardiovascular diseases.[17] A strong correlation has been demonstrated between small, dense, low-density lipoproteins (sdLDL) and CAS. Shoji et al.[18] previously investigated the correlation between carotid atherosclerosis and various lipid parameters in 326 consecutive subjects. Compared to LDL, apo B, apo A-I, non-HDL, and Tg levels, sdLDL levels have the highest correlation with carotid atherosclerosis (Spearman's $r=0.441$, $P<0.001$). According to the prospective study of Framingham offspring data, sdLDL demonstrated a strong association with atherosclerotic cardiovascular diseases.[17] Although sdLDL, which shows different lipid and protein components with the smallest molecular sizes and high affinity for proteoglycans in the arterial wall among LDL sub-fractions, is considered an ideal marker, it is very costly to determine the level by quantitative measurement.

Determination of sdLDL levels by lipoprotein separation is not a feasible method in daily practice. For this reason, studies have focused on searching for more cost-effective markers to correlate with sdLDL with similar sensitivity levels. Dobiasova et al.[5] aimed to determine atherogenic lipoprotein particles based on Tg and HDL plasma concentrations and obtained a statistically significant correlation with the studies. While conventional assessment of lipoprotein particle size distribution requires gradient gel electrophoresis, this described method accurately estimates sdLDL using routine serum lipid values.

There are many studies examining the correlations between lipid parameters and ischemic cerebrovascular diseases. Small-density lipoproteins support subclinical inflammation and atherosclerosis process by increasing oxidative stress, disrupting the endothelial structure, damaging cell DNA, and increasing lipid peroxidation activity. In our study, when Tg and HDL were evaluated apart from each other, no significant difference was observed in the levels of the CAS group. Tg/HDL was demonstrated as a predictor of CAS in patients with ischemic stroke in univariant and multivariate statistical analyses. In the literature, API has been presented as a parameter with similar predictive power but lower cost as sdLDL, the highly atherogenic LDL subgroup. In our study, API was observed as a predictor of CAS in individuals with ischemic stroke, correlating with previous studies.

Limitations

Our study has some limitations as well as strengths, such as the relatively high number of patients demonstrating the effects of API on CAS in ischemic SVO patients. Although the demographic characteristics were similar, the average age of the CAS group was statistically significantly higher since no propensity matching was performed in the patient recruitment. Lipid fractions such as lipoprotein a, apoprotein, and sdLDL could not be included in the study due to cost reasons. Another limitation of the study is that the data of patients with ischemic stroke were collected and designed retrospectively.

CONCLUSION

Today, when hyperlipidemia treatments are still discussed in the prevention of atherosclerosis, the search for more specific parameters other than classical lipid molecules continues. Our study aimed to determine the predictive variables of CAS in patients with ischemic stroke by examining the ratios of API and other non-classical parameters. Accordingly, API was demonstrated as a strong CAS predictor. In the study, more specific variables were observed as a result of the equations made with the lipid parameters that are frequently used in daily practice. Further prospective studies investigating the effects of API and other parameters on cardiovascular events may provide more effective data for the clinical approach.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Siirt University Medical Faculty Clinical Researches Ethics Committee (Date: 13.12.2022, Decision No: 62448).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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