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Monosit Sayısının Yüksek Yoğunluklu Lipoprotein Kolesteroel Oranı ve Ortalama Trombosit Hacmi, Karotis Arter Stenozunun Ciddiyeti ile İlişkili Olabilir

Monocyte Count to High-Density Lipoprotein Cholesterol Ratio and Mean Platelet Volume May Be Related to the Severity of Carotid Artery Stenosis

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ÖZET

Amaç: Karotis arter darlığının patofizyolojisi tam olarak anlaşılamamıştır. Araştırmalar, ortalama trombosit hacminin (MPV) trombosit aktivasyonu için potansiyel bir belirteç olduğunu ve ateroskleroz patofizyolojisinde anahtar bir faktör olduğunu göstermiştir. Son zamanlarda, monosit sayısının HDL'ye (MHR) oranı, hastalarda kardiyovasküler olayların bir prediktörü olarak tanımlanmıştır. Bu bulgular ışığında çalışmanın amacı, MPV ve MHR'nin CAD şiddeti ile olası ilişkisini araştırmaktır. Materyal-metot: Hastalar üç gruba ayrıldı: CAD≥%60 (40 hasta), CAD<% 60 (40 hasta) ve karotis aterosklerotik hastalığı olmayan (40 kişi). Hastaların demografik özellikleri, klinik özellikleri ve laboratuvar parametreleri gruplar arasında karşılaştırıldı. Bulgular: Kontrol grubunda MPV ve MHR seviyeleri CAD <60 grubuna göre daha düşük, CAD <60 grubunda CAD ≥60 grubuna göre daha düşüktü (p <0,001, p <0,001). Yüksek MPV (OR = 6.050;% 95 CI: 2.946-12.427; p <0.001) ve MHR (OR = 1.107;% 95 CI: 1.045 -1.159; p <0.001) seviyeleri çoklu lineer regresyon analizinden sonra ≥% 60 karotis arter darlığı için bağımsız prediktör olarak tespit edildi. Korelasyon analizinde MPV ile karotis arter darlığı oranı arasında pozitif korelasyon bulundu (p <0,001, r = 0,680). Sonuç: Çalışmamızda MPV ve MHR ile karotis arter hastalığı arasında potansiyel bir ilişki tespit edildi. Çalışmamız, karotis arter ateroskleroz patofizyolojisinin anlaşılmasına ve buna yönelik tedavilerin geliştirilmesine katkı sağlayabilir.

Anahtar Kelimeler: Karotis Arter Darlığı, Ortalama Trombosit Hacmi, Monosit-Yüksek Yoğunluklu Lipoprotein Oranı

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ABSTRACT

Objective: The pathophysiology of carotid artery stenosis (CAD) is not fully understood. Research has shown that mean platelet volume (MPV) is a potential marker for platelet activation and a key factor in the pathophysiology of atherosclerosis. Recently, the ratio of monocyte count to HDL (MHR) has been identified as a predictor of cardiovascular events in patients. In the light of these findings, the goal of this study was to evaluate the potential association of MPV and MHR with the severity of CAD.Material-Method: The patients were divided into three groups: CAD≥ 60% (40 patients), CAD <60% (40 patients) and no carotid atherosclerotic disease (40 individuals). Patients' demographic characteristics, clinical features and laboratory findings were compared between the groups.Results: MPV and MHR levels were lower in the control group than CAD <60 group and lower in CAD <60 group than CAD ≥60 group (p <0.001, p <0.001). Higher MPV (OR= 6.050; 95% CI: 2.946-12.427; p <0.001) and MHR (OR= 1.107; 95% CI: 1.045-1.159; p <0.001) levels were detected as an independent predictor for ≥60% carotid artery stenosis after multiple linear regression analysis. In the correlation analysis, a positive correlation was found between MPV and the rate of carotid artery stenosis (p<0.001, r=0.680). Conclusion: In our study, a potential relationship between MPV and MHR with carotid artery disease was determined. Our study may make contributions to understanding the pathophysiology of carotid artery atherosclerosis and developing treatments for it.

Keywords: Carotid artery stenosis, mean platelet volume, monocyte-to-high-density lipoprotein cholesterol ratio

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1. Objectıve

Cardiovascular disease may develop in patients with thickened carotid artery or atheromatous plaque, whose risk is four or more times greater than that of individuals without carotid target organ damage (1-3). Based on several epidemiological studies with larger sample sizes, there are strong evidences that carotid artery stenosis (CAD) is related to ischemic stroke events. Plaque morphology is more likely to contribute to the occurrence of stroke, with a severe carotid artery lesion (4). Research has shown that mean platelet volume (MPV) is a potential indicator for platelet activity and a key factor in the pathophysiology of atherosclerosis (5). Higher MPV values simply prompt acute coronary syndromes out of cardiovascular diseases, as well as hypertension, hyperlipidemia, and diabetes mellitus that are typical risks (6-9). However, studies examining the association of MPV with severe carotid artery atherosclerosis are limited, and the available data may conflict with each other (10). High-density lipoprotein (HDL) is an antioxidant and anti-inflammatory mediator, and it has a part in regulation of cholesterol flow between tissues, modulation of inflammation and oxidative stress (11-13). Circulating monocytes are a source of cytokines and molecules that cause extracellular matrix damage by interacting with platelet and endothelial cells, causing medial destruction in smooth muscle cells, leading to differentiation and apoptosis of cells, increased oxidative stress and tissue calcification (14). Recently, the monocyte to HDL ratio (MHR) has been defined as determinative of cardiovascular incidents in patients with chronic renal failure. Additionally, MHR has been determined to be associated with reduced aortic wall elasticity in coronary slow flow patients, stent thrombosis, metabolic syndrome and hypertension (15, 16).
In the light of these findings, the goal of this study was to research the potential connection of MHR and MPV with the severity of carotid artery stenosis.

2. Method

Presenting at the cardiology outpatient clinic from October 2016 to June 2020, the patients who had underwent brain neck computed tomography angiography (CTA) with suspicion of CAD or for cardiovascular risk assessment were included in study (17). The patients who, examined CT angiography for carotid arteries were divided into three CAD groups by the percentage of their atherosclerotic plaques: the first was below 60% (CAD<60) (Figure 2), the second was equal to and higher than 60% (CAD≥60) (Figure 1), and the third was 0% (CAD=0). 340 patients in total were retrospectively assessed until each group included 40 patients. Ethics Committee approval was obtained with the decision of Süleyman Demirel University School of Medicine Ethics Committee dated 16.04.2020 and numbered 114. We excluded patients who had an ongoing ischemic cerebrovascular event, ischemic cerebrovascular event irrespective of its sequelae, severe transient ischemic event or amaurosis fugax within 6 months before and the day when they presented at our cardiology outpatient clinic. Additionly, cancer, acute coronary syndrome, myocardial infarction, heart, kidney or liver failure, severe valvular disease, stroke (whether ischemic or not), chronic obstructive pulmonary disease, hematological disease, systemic inflammatory disease or an active infection in the patient's history was also regarded as an exclusion criterion. Hypertension was defined for anti-hypertensive drug users or patients whose blood pressure was equal to or greater than 140/90 mmHg. As for diabetes mellitus, the criteria were being and active user of oral antidiabetics and / or insulin, and a fasting glucose level of ≥126 mg/dL. Hyperlipidemia was identified when the total cholesterol level was ≥ 200 mg / dL, and coronary artery disease was identified when a major coronary artery plaque was present.

Computed Tomography Angiography Evaluations

For CAD measurement, the patients were followed by brain neck computed tomography angiography (CTA). We first accessed the antecubital vein and administered non-ionic contrast medium of 60 mL at a rate of 4.5 mL / sec, and then, a multidetector Siemens Somatom Definition AS (Siemens Erlangen, Germany) 128-slice CT machine was used to obtain the axial-plane CT images of the cerebral arteries. Technical parameters related to the brain neck CT angiography examination: Starting from the bifurcation level of the truncus pulmonalis in the caudal to the vertex in the superior, 0.6 mm slice thickness, 100 kV and effective milliamper seconds were obtained with mAs 170 mAs, FOV (Field of View) at an average of 190 mm and pitch value of 0.8.

The images obtained in the axial were reformatted to sagittal images for measurement. Vascular plaques and stenosis were assessed based on these reformatted sagittal images. The NASCET (North American Symptomatic Carotid Endarterectomy Trial) classification, which is a modern evaluation system that is adopted to evaluate CAD severity, was used for classification of carotid artery stenosis (18). We made the classification considering higher stenotic lesions for multiple stenotic lesions or bilateral stenosis.

Statistical Analysis

Data analysis was performed using the SPSS 22.0 statistical package software (SPSS Inc., Chicago, IL, USA). The continuous parameters are shown as mean ± SD, while the categorical variables are presented as frequencies and percentages. Number of each group was adjusted as 40 patients. Because we calculated the minimum number of individuals that should be sampled with 90% power and 0.05 Type-I error as at least 40 (R 3.0.1. open source program). The primary effect variable was determined as the CAD rate 1% change was accepted as clinically relevant. For comparison of the normally distributed variables, Student's t-test was used. Mann-Whitney U test was preferred for the non-normally distributed variables in 2-group comparisons. Among three groups, one-way analysis of variance (ANOVA) was used for the normally distributed variables. For the categorical variables, $\chi 2$ (Chi-squared) test was used, or if appropriate, Fisher's exact test. To evaluate the relationships the continuous variables, Pearson's correlation coefficients were examined. Spearman's correlation analysis was applied for the discontinuous and categorical parameters. Univariate and multiple linear regression analyses were performed using the factors and the basic clinical risk factors found significant as shown in Table 1 to determine the factors affecting carotid artery stenosis above 60%. The statistical significance level was determined as $p<0.05$, and the confidence interval was 95%.

3. Results

The laboratory parameters and demographic characteristics of the groups are shown in Table 1. When the demographic features were evaluated, there was no difference between the groups in terms of sex, age, diabetes, hyperlipidemia, peripheral artery disease body mass index, ejection fraction, and coronary artery disease. Hypertension was lower in the control group than CAD <60 group and lower in CAD <60 group than CAD ≥60 group ($p <0.001$, $p <0.001$). No difference was determined between the laboratory parameters except uric acid. Uric acid leves was lower in the control group than CAD <60 group ($p=0.025$). MPV level was lower in the control group than CAD <60 group and lower in CAD <60 group than CAD ≥60 group ($p <0.001$, $p <0.001$). MHR level was lower in the control group than CAD <60 group and lower in CAD <60 group than CAD ≥60 group ($p <0.001$, $p <0.001$) (Table 1).

We performed univariate and multiple linear regression analyses for predictors of ≥60% carotid artery stenosis as depicted in Table 1 (Table 2). Hypertension (OR= 2.523; 95% CI: 0.976-6.521; $p=0.048$), and higher MPV levels (OR= 6.050; 95% CI: 2.946-12.427; $p <0.001$) and higher MHR (OR= 1.107; 95% CI: 1.045-1.159; $p <0.001$) were detected as independent predictors for ≥60% carotid artery stenosis after multiple linear regression analysis.

In correlation analysis, a positive correlation was found between MPV and the rate of carotid artery stenosis ($p<0.001$, $r=0.680$) (Figure 3).

4. Discussion

Research has shown that cardiovascular complications may occur from higher platelet activation and aggregation (5, 19). Platelet function may be easily and accurately evaluated by estimating platelet size typically via the quantification method of MPV. Platelets display heterogeneous characteristics in terms of size, density and reactivity. With a greater mass larger platelets have higher metabolic and enzymatic activity (20). In comparison to smaller platelets, they can aggregate with collagen more quickly thanks to greater numbers of granules, expressing a greater number of glycoprotein receptors (Ib and IIb/IIIa) due to higher thromboxane A2 levels (21). It is assumed that large platelets are biochemically, functionally and metabolically more active by means of high granule concentration (22). Platelet morphology and physiology are determined during the lysis of the precursor cells, megakaryocytes. Increased megakaryocyte ploidy has been found to be associated with an increase in megakaryocyte and platelet volume (22). On the other hand, consumption of small platelets during acute ischemia may also lead to an increase in MPV due to compensatory production (22). Based on this, it was suggested that MPV might be a marker for platelet activity and a prognostic factor for atherosclerosis (23). Because of its importance in the repair of damaged blood vessels, the marker of age or increased production of platelets is useful in many clinical disorders where vascular damage is significant.

Table 1. Baseline characteristics and laboratory parameters of the study groups (n=120)

Variables	Control (n=40)	Carotid artery stenosis <60 % (n=40)	Carotid artery stenosis ≥60% (n=40)	p value*	p value$^{\alpha}$	p value$^{\beta}$	p value$^{\gamma}$
Age,years	54.9 ± 8.7	57.2 ± 8.2	60.4 ±8.2	0.069	-	-	-
Female, n(%)	18 (45.0)	16 (40.0)	14 (35.0)	0.659	-	-	-
BMI, kg/m^2	28.1± 2.4	28.1 ± 2.8	28.4 ± 2.7	0.868	-	-	-
Diabetes Mellitus, n(%)	9 (22.5)	10 (25.0)	10 (25.0)	0.956	-	-	-
Hypertension, n(%)	6 (15.0)	14 (35.0)	20 (50.0)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Hyperlipidemia, n(%)	8 (20.0)	8 (20.0)	10 (25.0)	0.822	-	-	-
Smoking, n(%)	16 (40.0)	14 (35.0)	17 (62.5)	0.783	-	-	-
Coronary artery disease, n(%)	6 (15.0)	9 (22.5)	6 (15.0)	0.799	-	-	-
Peripheral vascular disease, n(%)	3 (7.5)	4 (10.0)	5 (12.5)	0.757	-	-	-
Carotid artery stenosis, (%)	0 ± 0.00	31.1 ± 11.7	68.7 ± 12.5	**<0.001**	**<0.001**	**<0.001**	**<0.001**
LVEF, %	57.4 ± 5.3	57.5 ± 6.4	58.1 ± 4.8	0.678	-	-	-
Glucose, mg/dL	112.1 ± 46.6	116.2 ± 58.1	116.8 ± 53.1	0.889	-	-	-
Creatinine, mg/dL	1.00 ± 0.17	0.99 ± 0.23	1.08 ± 0.26	0.531	-	-	-
Uric Acid, mg/dl	5.0 ± 1.8	6.0 ± 2.3	6.7 ± 2.1	**0.002**	0.198	**<0.001**	**0.025**
WBC,10^3/mm^3	9.8 ± 2.4	9.0 ± 2.0	9.4 ± 2.3	0.236	-	-	-
Hemoglobin, g/dL	13.3 ± 1.9	13.7 ± 1.3	13.5 ± 1.8	0.459	-	-	-
Platelet, 10^3/mm^3	240.5 ± 50.1	237.1 ± 80.3	247.5 ± 65.1	0.731	-	-	-
CRP,mg/L	3.4 ± 1.7	3.7 ± 2.1	4.4 ± 2.6	0.470	-	-	-
Total cholesterol, mg/dL	189.1 ± 94.0	190.0 ± 55.1	183.0 ± 39.4	0.888	-	-	-
LDL-C, mg/dL	114.9 ± 57.3	111.7 ± 45.9	114.6 ± 34.0	0.951	-	-	-
HDL-C, mg/dL	45.6 ± 24.5	44.3 ± 11.1	42.0 ± 6.8	0.780	-	-	-
Triglyceride, mg/dL	184.1± 32.3	176.1 ± 96.0	142.1 ± 86.0	0.336	-	-	-
MPV (fl)	8.25 ± 0.23	9.36 ± 0.63	9.89 ± 0.82	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Monocyte /HDL ratio	0.41± 0.21	0.46 ± 0.15	0.53 ± 0.18	**<0.001**	**<0.001**	**<0.001**	**<0.001**

Data are given as mean ± SD, n (%) or median (lower-upper limit). BMI body mass index; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; WBC, white blood cell; MPV, Mean platelet volume. Carotid artery stenosis rate was calculated according to NASCET.

* p value between all groups

$^{\alpha}$ p value between carotid artery stenosis ≥60% and carotid artery stenosis <60% groups,

$^{\beta}$ p value between carotid artery stenosis ≥60% and control groups,

$^{\gamma}$ pvalue between carotid artery stenosis <60% and control groups.

In studies conducted up to date, it has beenshown that acute myocardial infarction and congestive heart failure could raise MPV in unstable angina pectoris (24-27). Increased MPV levels were found to be associated with high thromboxane A2, serotonin, betathromboglobulin, and procoagulant membrane protein levels (5). One of the initiating pathophysiological mechanisms in carotid artery atherosclerosis is

endothelial dysfunction. The regulating mediators for endothelium, vascular tone, vascular proliferation platelet adhesion, fibrinolysis, and inflammation are locally produced to maintain vascular homeostasis (4). Impairment of endothelial function negatively affects these events and creates cardiovascular risk. Endothelial dysfunction may be associated with increased MPV level and therefore carotid artery atherosclerosis through these mediators (28, 29). Increased MPV levels have been associated with many rheumatological diseases and are now described as an inflammatory marker. In atherosclerotic diseases with inflammation, such as coronary artery disease and coronary artery ectasia, MPV levels have been found to be increase (30, 31). Carotid artery atherosclerosis is now known to play a role in inflammation, and new treatment targets focus on inflammation (4).

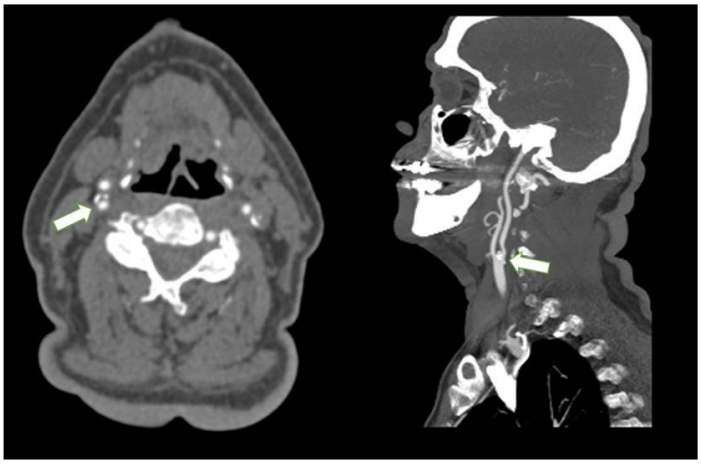

Figure 1. In the axial (left) and sagittal (right) plane Brain + Carotid (Brain + neck) CT angiography examination, a mixed plaque (white arrow) that causes 80-90% stenosis in the left ICA proximal part is observed.

Oxidative stress is an important mechanism in atherosclerosis. (1). Endothelial-induced oxidative stress triggers myofibroblast activation and calcification. (13). HDL has been known to be a strong antioxidant molecule primarily through reduction of cellular uptake by the monocyte macrophage system mediated by inhibiting oxidation of LDL. (32). Oxygen radicals and transition metals resulting from the metabolism have a role in oxidative stress and HDL has been shown to play an antioxidant role by showing chelation characteristics due to the presence of mediators such as ceruloplasmin on the lipoprotein surface (33). Lipid peroxidation products are derived from oxidized low-density lipoprotein and have been shown to be strongly cytotoxic and susceptible to process of atherosclerosis. In vitro studies on HDL have revealed that uptake of hydroperoxides from oxidized membranes could potentially ensure, a pathway for evacuation or detoxification (33). Therefore, the balance between the number of monocytes and HDL may clarify the effect of oxidative stress in CAD.

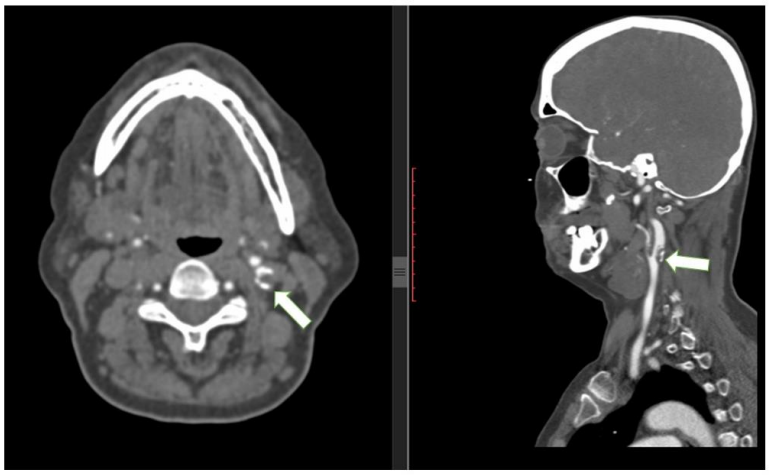

Figure 2. In the axial (left) and sagittal (right) plane Brain + Carotid (Brain + neck) CT angiography examination, a mixed plaque (white arrow) is observed in the proximal part of the right ICA causing approximately 40% stenosis.

Table 2. Multivariate logistic regression analysis showing the predictors for ≥60% carotid artery stenosis

Variables	Univariable Beta (95% CI)	p value	Multivariable Beta (95% CI)	p value
Hypertension	3.000 (1.348-6.678)	**0.007**	2.523 (0.976- 6.521)	**0.048**
Uric Acid	1.263 (1.058-1.507)	0.098	-	-
MPV	6.221 (3.070-12.607)	**<0.001**	6.050 (2.946-12.427)	**<0.001**
Monocyte /HDL ratio	1.201 (1.110-1.393)	**<0.001**	1.107 (1.045-1.159)	**<0.001**

Limitations of the study

In our study, the sample size was relatively small. MHR and MPV analyses were retrospective and patients do not have long-term follow-up. In our study, blood samples taken into tubes with EDTA were evaluated by waiting for 2 hours. Although methodological changes in the measurement of mean platelet volume do not allow setting standard normal limits, each laboratory can determine its own normal limits with its own method. In addition to MPV, which is considered as a rough indicator for platelet function, the measurement of advanced platelet function parameters, which are more expensive and not widely used, can also provide more information in terms of pathogenesis and risk. The number of patients is relatively low. Carotid artery evaluation was performed by CT angiography only. More specific methods have not been evaluated. NASCET scoring system has technical limitations, it is difficult to correlate statistically, especially in biletareal stenosis.

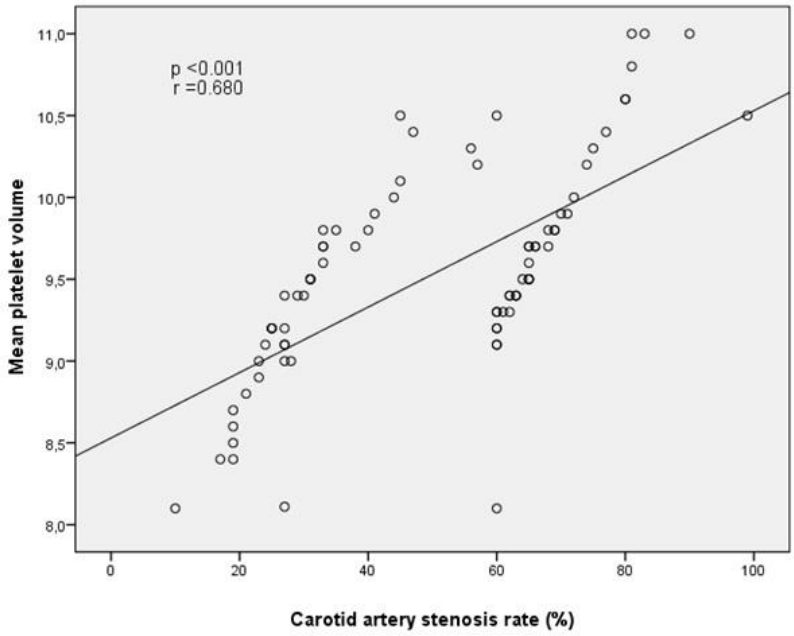

Figure 3. Correlation between mean platelet volume and carotid artery stenosis

5. Conclusion

In our study, a potential relationship between MPV, MHR and carotid artery disease was determined. Our study may make contributions to understanding the pathophysiology of carotid artery atherosclerosis and developing treatments for it.

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