RESEARCH ARTICLE / *Araştırma Makalesi*

A Promising Marker for Carotid Artery Disease: Monocyte to High-density Lipoprotein Cholesterol Ratio

Karotis Arter Hastalığı için Umut Verici Marker: Monosit Yüksek Yoğunluklu Lipoprotein Kolesterol Oranı

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Abstract

Objective	The aim of our study was to evaluate the relation between monocyte/high-density lipoprotein cholesterol (HDL-C) ratio value and carotid artery stenosis in patients who underwent carotid angiography.
Materials and Methods	To our study, 103 participants were enrolled (70 patients, 33 healthy individuals) who attended the cardiovascular surgery policlinic and had carotid angiography in between January 2017 and June 2018. Participants were divided into two groups, who have carotid artery disease and who don't. Peripheral venous blood results, taken from all patients before angiography for hematologic examination, were evaluated. Groups were compared according to their monocyte/high-density lipoprotein cholesterol (HDL-C) values and other hematologic results.
Results	Monocyte/high-density lipoprotein cholesterol (HDL-C) ratio and monocyte values were found to be higher in the group with a carotid artery disease compared to the group with a normal carotid angiography (0.018±0.009 vs. 0.013±0.007 p= 0.008; 0.67±0.28 vs. 0.51±0.24 p=0.007). There was no significant difference between groups considering demographic features and other hematological paramaters.
Conclusions	In our study, it was shown that high monocyte/high-density lipoprotein cholesterol (HDL-C) ratio value could be a predictor for the diagnosis of obstructive carotid artery disease.
Keywords	Carotid artery disease; Monocyte/high-density lipoprotein cholesterol (HDL-C) ratio; Atherosclerosis risk factors.

Öz

Amaç	*Çalışmamızın amacı karotis arter angiografisi yapılan hastalarda monosit/yüksek yoğunluklu lipoprotein kolesterol oranı değerlerinin karotis arter stenozu ile ilişkisini retrospektif olarak araştırmaktı.*
Gereç ve Yöntemler	*Çalışmamıza Ocak 2017 ile Haziran 2018 yılları arasında kalp ve damar cerrahisi polikliniğine başvuran ve karotis arter angiografisi yapılan 103 (70 hasta, 33 sağlıklı) hasta dahil edildi. Karotis arter hastalığı olanlar ve olmayanlar diye iki gruba ayrıldı. Tüm hastaların hematolojik değerlerine bakılması için angiografi öncesi alınan periferik venöz kan sonuçları tarandı. Gruplar monosit/yüksek yoğunluklu lipoprotein kolesterol oranı ve diğer hematolojik sonuçlar açısından karşılaştırıldı.*
Bulgular	*Monosit/yüksek yoğunluklu lipoprotein kolesterol oranı ve monosit değeri karotis arter hastalığı olanlar grubunda karotis arter angiografisi normal çıkan gruba göre anlamlı olarak yüksek bulundu (0.018±0.009 vs. 0.013±0.007 p= 0.008; 0.67±0.28 vs. 0.51±0.24 p=0.007). Diğer hematolojik parametreler ve demografik veriler açısından gruplar arasında anlamlı bir farklılık yoktu.*
Sonuç	*Çalışmamızda yüksek monosit/yüksek yoğunluklu lipoprotein kolesterol oranının karotis arter hastalığı tanısında bir öngördürücü olabileceği gösterildi.*
Anahtar Kelimeler	*Karotis arter hastalığı; monosit/yüksek yoğunluklu lipoprotein kolesterol oranı; Ateroskleroz risk faktörleri.*

Introduction

Carotid artery stenosis is a major risk factor for stroke. The cause of stroke in a great many of the patients is ischemia, in one-third of this group of patients it is carotid artery disease.[1,2] Atherosclerosis is usually the cause of carotid artery stenosis and occlusion. Atherosclerosis is a complex inflammatory process. In this process, monocytes and macrophages play a key role in each stage of inflammation and the release of proinflammatory cytokines.[3] These immune cells cause an inflammatory response and tissue remodelling in atherosclerotic lesions.[4,5] Especially activated monocytes effect on the release of inflammatory cytokines during the progression of chronic inflammation and cardiovascular disease.[6]

It is known that high-density lipoprotein cholesterol (HDL-C) is protecting the endothelium against the destructive effects of low-density lipoprotein cholesterol (LDL-C) as well as oxidation.[7] The ratio of the number of monocytes to HDL-C level, as known as monocyte/HDL-C ratio (MHR), is a recently detected inflammatory indicator.[8]

In our study, our aim was to research the relation between MHR and carotid artery stenosis retrospectively at the patients who admitted to cardiology and cardiothoracic surgery policlinic in between 2017 and 2018.

Materials and Methods

In this study, 103 patients undergoing carotid angiography at Kahramanmaraş Sütçü İmam University Research Hospital between January 2017 and June 2018 were evaluated retrospectively. This was planned as a cross sectional study. Patients who have no atherosclerotic lesions are accepted as normal and are assigned to the control group. Patients who have a lesion on the surface of the carotid artery, regardless of the significance of the stenosis it causes, are assigned to the patient group. Blood tests, clinical conditions and angiographic images of all patients are examined.

Patients who had a previous cerebrovascular event, acute cardiovascular event, trauma, who has renal failure or liver failure, who use immunosuppressant drugs, anti-inflammatory drugs or steroids are not included in our study. The demographic characteristics of the patients involved in the study such as gender, age, hypertension, diabetes, dyslipidemia and family stories as well as their laboratory tests are evaluated. The Kahramanmaraş Sütçü İmam University ethics committee approved the study with an issue number 11, dated August 29, 2018.

Biochemical analysis

Before the carotid angiography procedure, retrospectively full blood counts and biochemical parameters in blood samples taken from the patients are evaluated. For full blood count tests, blood is taken into ethylenediaminetetraacetic acid (EDTA) containing tubes and evaluated by the hematology analyser Sysmex XN-1000 (Sysmex Europe GmbH, Sysmex Corporation, Hamburg, Germany). For biochemical evaluation of the glucose, urea, creatinine, AST, ALT levels and lipid profile, blood samples are taken into dry tubes and evaluated by automatic analysis device Cobas®8000 (Roche Diagnostics International Ltd., Rotkreuz, Switzerland). MHR is calculated by dividing the monocyte count to HDL-C.

Angiographic analysis

All angiographic images are taken by using GeGE angiography device, through a retrograde femoral arterial access. Carotid arteries images are taken bilaterally. Patients who have no carotid arterial disorder are accepted as normal. Patients who have an atherosclerotic lesion, regardless of the severity of the stenosis, are assigned to the carotid artery patient group.

Statistical analysis

Continuous variables that fit a normal distribution are expressed as mean ± standard deviation, continuous variables that don't fit a normal distribution are expressed by using median and change in quarters. Categorical variables are expressed by absolute value and percentage. Whether

the continuous variables fit a normal distribution or not, is evaluated by the Kolmogorov-Smirnov test. Continuous variables in between groups that don't fit a normal distribution are evaluated by Mann-Whitney U test, while the continuous variables that fit a normal distribution are evaluated by independent samples t-test. Categorical variables are evaluated by Chi-square test. All statistical evaluations are made by using SPSS 21 program (Statistical Package for the Social Sciences, version 21.0, SSPS Inc., Chicago, IL, USA). P value < 0.05 is accepted as significant.

Results

A total of 103 patients were included in the study; 70 patients with angiographically proven significant carotid artery disease and 33 patients with normal carotid artery. When the clinical and demographical features of the patients were compared, there was no significant difference with respect to age, gender, hypertension and diabetes. When the laboratory results of the patients were compared, all variables were found to be similar except monocyte/HDL-C ratio and monocyte count. Monocyte/HDL-C ratio and monocyte count was found to be significantly higher in patients with carotid artery disease as compared to the patients having normal carotid artery. (0.018±0.009 vs. 0.013±0.007, p= 0.008; 0.67±0.28 vs. 0.51±0.24, p=0.007 respectively). Basic demographic, clinical and laboratory values are shown in Table 1. The distribution of monocyte/HDL-C ratio (MHR) is shown in Figure 1.

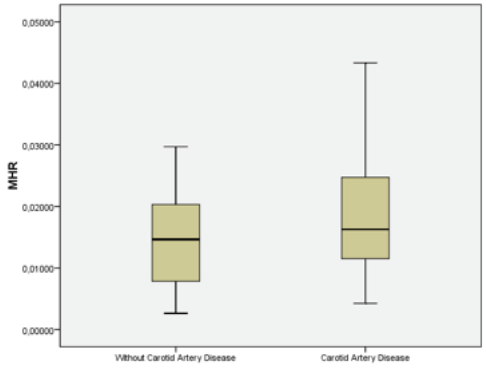

Figure 1: Distribution of MHR between the patients with and without carotid artery disease.

Table 1:Demographic, clinic and laboratory characteristics of the groups

	Carotid Artery Disease (n=70)	Without Carotid Artery Disease (n=33)	P value
Age,years	72.24±8.12	69.58±9.14	0.059
Male/female,n	46/24	22/11	0.924
Hypertension, n, (%)	28 (40.00 %)	11 (33.33 %)	0.664
Diabetes mellitus, n, (%)	17 (24.29%)	10 (30.30%)	0.632
BUN, median (range), (mg/dl)	19.00(7.00-86.00)	17.00(10.00-56.00)	0.632
Creatinine, mean±SD, (mg/dl)	0.93±0.22	0.86±0.23	0.207
Triglycerides, median (range) (mg/dL)	150.00 (34.00-624.00)	139.00 (48.00-635.00)	0.964
HDL cholesterol, mean±SD, (mg/dL)	38.81±9.08	40.78±9.24	0.248
LDL cholesterol, mean±SD, (mg/dL)	107.46±38.14	103.52±29.92	0.600
ALT , median (range), IU/L	23.00 (7.00-85.00)	20.00 (5.00-55.00)	0.079
AST , median (range), IU/L	22.00 (6.00-57.00)	21.00 (4.00-36.00)	0.078
Hemoglobin, mean±SD gr/dl	13.22±1.08	13.98±1.14	0.105
Hemotocrite, mean±SD	39.64±5.22	41.18±5.06	0.158
Platelet count x103/L, median (range)	219.00 (65.00-520.00)	224.00 (108.00-517.00)	0.779
RDW, mean±SD, (mg/dl)	43.25±4.12	44.69±7.23	0.297
MPV median (range)	10.32 (8.54-17.08)	10.66 (8.61-13.30)	0.564
RBC, mean±SD, (mg/dl)	4.64±0.61	4.89±0.63	0.176
Monocyte count x103/L, mean±SD	0.67±0.28	0.51±0.24	0.007
MHR, mean±SD	0.018±0.009	0.013±0.007	0.008

BUN: Blood urea HDL: High-density lipoprotein cholesterol LDL: Low-density lipoprotein cholesterol ALT: Alanin amino transferaz AST: Aspartate aminotransferase RDW: Red cell distribution width MPV: Mean Platelet Volume RBC: Red blood cell MHR: Monocyte/high-density lipoprotein cholesterol (HDL-C) ratio

Discussion

In this study, we tried to determine the potential role of MHR in predicting the carotid artery disease by comparing the MHR values between patients who have carotid artery disease and who have a normal carotid artery. It has been claimed that HDL-C has monocyte activating effect and suppressor effects on differentiation and proliferation

of progenitor cells in addition to its anti-inflammatory and anti-oxidant actions.[9,10] MHR is a new parameter used to predict morbidity and mortality in chronic inflammatory conditions such as cardiovascular disease, metabolic syndromes and hypertension.[11-13]

Carotid atherosclerosis is an important risk factor for the development of acute ischemic stroke. The role of macrophages and monocytes is well known in the development and progression of atherosclerosis.[14,15] Following endothelial dysfunction, monocytes adhere to the endothelium tightly and migrate into subendothelial layer. Then, they maturate into macrophages which are the precursors of foam cells. Foam cells secrete pro-inflammatory cytokines that induce the local inflammatory response around the atherosclerotic lesion such as matrix metalloproteinases, tissue factors and growth factors.[15,16] It is seen that macrophages and monocytes play a role in all stages; from the formation of the fatty streak to the formation of atherosclerosis and its progression. Thus, the monocyte count can be an indicator of the development of atherosclerotic plaques.[15] In a study conducted by Qiao and his colleagues, a relation between the monocyte count and atherosclerosis has been shown in rats with colony stimulating factor deficiency.[17]

HDL-C has well-known anti-inflammatory and antioxidant effects as well as antithrombotic effects. These effects vary with the levels of HDL-C.[18] There also is an interaction in between HDL-C and monocytes. It limits the inflammatory response that occurs while monocytes differentiate into macrophages.[19] It is shown that the increase in HDL-C levels effects on the hemopoietic system by decreasing monocyte production, mobilization and progenitor cell proliferation.[20,21]

MHR is reported as an inflammatory indicator in previous studies. In a study by Kanbat and his colleagues, high levels of MHR is related to high cardiovascular risk in the prognosis of chronic renal disease.[22] Tekkesin and his colleagues have shown in their study that MHR levels were significantly higher in patients developing postoperative atrial fibrillation, which could cause serious mortality and morbidity after cardiovascular surgery, as compared to the patients without postoperative atrial fibrillation.[23] In another study conducted by Bolayir et al., lower HDL-C levels and higher monocyte counts were found in patients who are hospitalized for acute stroke as compared to the control group. The authors also claimed that it was an independent risk factor for 30 days mortality.[24] Similarly, in a study conducted by Zhang et al. including 3798 patients who have undergone coronary angiography, it has been shown that MHR value is an independent predictor of a major cardiovascular event (acute myocardial infection, unstable angina, stroke, heart failure and unexpected vascularization).[25]

When all the studies were evaluated, it is shown that MHR value is related to systemic inflammation and endothelial dysfunction and is attributed as an inflammatory marker. Our study has less number of patients compared to the previous studies in the literature. Based on our study, we conclude that the significant high values of MHR found in patients with obstructive carotid artery disease as compared to the patients with normal carotid artery can be an independent predictive marker but still cannot be claimed as a diagnostic marker.

Conclusion

Carotid artery disease is a preventable and treatable disease if diagnosed early. MHR value is not only an easy test but also doesn't require extra cost. In our study, MHR value is found to be high in patients who have a carotid artery lesion. More detailed and extensive multicentric prospective studies are needed to support our results.

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met Kirişci Writing the Article: Mehmet Kirişci ; Critical Review: Mehmet Kirişci,

References

1. *Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/ SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. Circulation 2011;124:e54-130.*
2. *Tendera M, Aboyans V, Bartelink ML, Baumgartner I, Clement D, Collet JP, et al. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). Eur Heart J 2011;32:2851-2906.*
3. *Hansson GK, Libby P, Schonbeck U, Yan ZQ. Innate and adaptive immunity in the pathogenesis of atherosclerosis. Circ Res 2002;91:281–291.*
4. *Hansson G. Inflammatory mechanisms in atherosclerosis. J Thromb Haemost 2009;7:328–331.*
5. *Aşkın L, Çetin M, Türkmen S, Taşolar H, Aktürk E. The relationship between monocyte/high-density lipoprotein ratio and Selvester QRS score in patients with STEMI. Turk Kardiyol Dern Ars 2018;46(4):260-267.*
6. *Olivares R, Ducimetière P, Claude JR. Monocyte count: a risk factor for coronary heart disease? Am J Epidemiol 1993;137 (1):49–53.*
7. *Hafiane A, Genest J. High density lipoproteins: measurement techniques and potential biomarkers of cardiovascular risk. BBA Clin 2015;3:175–188.*
8. *Zhang Y, Li S, Guo YL, Wu NQ, Zhu CG, Gao Y, et al. Is monocyte to HDL ratio superior to monocyte count in predicting the cardiovascular outcomes: evidence from a large cohort of Chinese patients undergoing coronary angiography. Ann Med 2016;48(5):305–312.*
9. *Parthasarathy S, Barnett J, Fong LG. High-density lipoprotein inhibits the oxidative modification of low-density lipoprotein. Biochim Biophys Acta 1990;1044:275-283.*
10. *Westerterp M, Gourion-Arsiquaud S, Murphy AJ, Shih A, Cremers S, Levine RL,et al. Regulation of hematopoietic stem and progenitor cell mobilization by cholesterol efflux pathways. Cell Stem Cell 2012;11:195-206.*
11. *Cetin MS, Ozcan Cetin EH, Kalender E, et al. Monocyte to HDL cholesterol ratio predicts coronary artery disease severity and future major cardiovascular adverse events in acute coronary syndrome. Heart Lung Circ 2016;25:1077-1086.*
12. *Aydin E, Ates I, Fettah Arikan, et al. The ratio of monocyte frequency to HDL cholesterol level as a predictor of asymptomatic organ damage in patients with primary hypertension. Hypertens Res 2017;40:758-764.*
13. *Vahit D, Mehmet KA, Samet Y, et al. Assessment of monocyte to high density lipoprotein cholesterol ratio and lymphocyteto-monocyte ratio in patients with metabolic syndrome. Biomark Med 2017;11:535-540*
14. *Ren H, Liu X, Wang L,Gao Y. Lymphocyte-to-monocyte ratio: a novel predictor of the prognosis of acute ischemic stroke. Journal of Stroke And Cerebrovascular Diseases 2017;26(11): 2595–2602*
15. *Ancuta P, Wang J, Gabuzda D. CD 16 monocytes produce IL-6,CCL2 and matrix metalloproteinase -9 upon interaction with CX3 CL1- expressing endoteial cells. J Leukoc Biol 2006;80:1156-1164.*
16. *Urra X, Villamor N, Amaro S, et al. Monocyte subtypes predict clinical course and prognosis in human stroke. J Cereb Blood Flow Metab 2009;29:994-1002.*
17. *Qiao JH, Tripathi J, Mishra NK, Cai Y, Tripathi S, Wang XP, et al. Role of macrophage colony-stimulating factor in atherosclerosis: studies of osteopetrotic mice. Am J Pathol 1997;150:1687–1699.*
18. *Murphy AJ, Woollard KJ. High-density lipoprotein: a potent inhibitor of inflammation. Clin Exp Pharmacol Physiol 2010;37:710–718.*
19. *Murphy AJ, Woollard KJ, Hoang A, Mukhamedova N, Stirzaker RA, McCormick SPA, et al. High-density lipoprotein reduces the human monocyte inflammatory response. Arterioscler Thromb Vasc Biol 2008;28:2071–2077.*
20. *Westerterp M, Gourion-Arsiquaud S, Murphy AJ, Shih A, Cremers S, Levine RL, et al. Regulation of hematopoietic stem and progenitor cell mobilization by cholesterol efflux pathways. Cell Stem Cell 2012;11:195–206.*
21. *Wang N, Lan D, Chen W, Matsuura F, Tall AR. ATP-binding cassette transporters G1 and G4 mediate cellular cholesterol efflux to highdensity lipoproteins. Proc Natl Acad Sci U S A 2004;101:9774–9779.*
22. *Kanbay M, Solak Y, Unal HU, Kurt YG, Gok M, Cetinkaya H, et al. Monocyte count/HDL cholesterol ratio and cardiovascular events in patients with chronic kidney disease. Int Urol Nephrol 2014;46:1619–1625.*
23. *Tekkesin AI, Hayiroglu MI, Zehir R, Turkkan C, Keskin M, Cinier G, Alper AT. The use of monocyte to HDL ratio to predict postoperative atrial fibrillation after aortocoronary bypass graft surgery. North Clin Istanb 2017;4(2):145-150.*
24. *Bolayir A, Gokce SF, Cigdem B, Bolayir HA, Yildiz OK, Bolayir E, Topaktas SA. Monocyte/high-density lipoprotein ratio predicts the mortality in ischemic stroke patients. Neurol Neurochir Pol 2018;52(2):150-155.*
25. *Zhang Y, Li S, Guo YL, Wu NQ, Zhu CG, Gao Y, Xu RX, Dong Q, Liu G, Sun J, Li JJ. Is monocyte to HDL ratio superior to monocyte count in predicting the cardiovascular outcomes: evidence from a large cohort of Chinese patients undergoing coronary angiography. Ann Med 2016;48(5):305-312.*