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Araştırma Makalesi / Research Article

Monocyte to HDL Ratio in The Prediction of Carotid Artery Intima-Media Thickness

Karotis Arter Intima-Media Kalınlığının Tahmininde Monosit-HDL Oranı

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Abstract

Aim: In this study, we aimed to determine whether an increased monocyte count to high-density lipoprotein (MHR) would predict increased carotid intima-media thickness (IMT).
Material and Method: All consecutive subjects presenting to the cardiology outpatient clinic of our institute were enrolled in this cross-sectional study. Subjects with cardiovascular and inflammatory diseases were excluded. Subjects were divided into two groups according to carotid IMT: those with carotid IMT >0.9 mm (increased) and those with carotid IMT ≤0.9 mm (normal). The difference in MHR between the two groups was the primary outcome measure of the study.
Results: The MHR of the subjects with increased IMT was significantly higher than that of subjects with normal IMT (16.7 ± 5.7 vs. 12.8 ± 5.5, p <0.001). Logistic regression analysis demonstrated that age (OR: 1.202, 95% CI: 1.126-1.284, p<0.001) and MHR (OR: 1.190, 95% CI: 1.097-1.291, p<0.001) were significant predictors for a carotid IMT of >0.9 mm. ROC curve analysis revealed an MHR value of 13.4 as a cut-off in the identification of subjects that had increased IMT, with a sensitivity of 72% and specificity of 60.7%.
Conclusion: The inflammation marker MHR can be used as a simple and cost-effective marker to predict increased carotid IMT which is accepted as the indicator of subclinical atherosclerosis.

Keywords: Coronary artery disease, monocytes, high density lipoprotein, HDL, carotid intima-media thickness

Öz

Amaç: Bu çalışmada, artmış monosit sayısının yüksek yoğunluklu lipoprotein düzeylerine oranı (MHO)'nun artmış karotis intima-media kalınlığı (İMK)'yi yordayıp yordamayacağını belirlemeyi amaçladık.
Materyal ve Metot: Kurumumuzun kardiyoloji polikliniğine ayaktan başvuran ardışık tüm olgular bu kesitsel çalışmaya alındı. Kardiyovasküler ve enflamatuar hastalıkları olan olgular hariç tutuldu. Olgular karotis İMK'ye göre iki gruba ayrıldı: karotis İMK>0,9 mm (artmış) ve karotis İMK≤0.9 mm (normal) olanlar. MHO'daki iki grup arasındaki fark, çalışmanın birincil sonuç ölçütüdür.
Bulgular: Artmış İMK'ye sahip olguların MHO'su, normal İMK'ye sahip olgulardan anlamlı olarak daha yüksekti (16,7 ± 5,7'ye karşı 12,8 ± 5,5; p<0,001). Lojistik regresyon analizi, yaşın (OR: 1,202, 95% CI: 1,126-1,284; p<0,001) ve MHR (OR: 1,190, 95% CI: 1,097-1,291; p<0,001)'nin >0,9 mm'lik bir karotis İMK'si için önemli prediktörler olduğunu gösterdi. ROC eğrisi analizi, %72 duyarlılık ve %60,7 özgüllük ile 13,4'lük bir MHO kesme değerinin artmış İMK'nin saptanmasında kullanılabileceğini gösterdi.
Sonuç: Enflamasyon belirteci MHO, subklinik aterosklerozun göstergesi olarak kabul edilen artmış karotis İMK'sini tahmin etmek için basit ve maliyet-etkin bir belirteç olarak kullanılabilir.

Anahtar Kelimeler : Koroner arter hastalığı, monositler, yüksek yoğunluklu lipoprotein, HDL, karotis intima-media kalınlığı

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INTRODUCTION

Coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide. Despite the gradual decline in the mortality of CAD over the last decades, particularly in the western world, CAD is still responsible for one-third of all deaths among individuals older than 35 years (1-3). The overall disease burden and related morbidity and mortality of CAD have led to a search for solutions that could aid early diagnosis and management. It is now well-known that early diagnosis and interventions, even in subjects without symptoms, improves prognosis. Carotid artery intima-media thickness (IMT) is utilized as a non-invasive measurement of early atherosclerotic changes in the carotid artery wall. It is a surrogate marker for subclinical cardiovascular disease and cardiovascular events (4, 5). The ACCF/AHA guidelines recommend using carotid IMT for the assessment of individuals presenting with an intermediate risk of CAD (6). Despite its wide availability, measurement of carotid IMT is time-consuming and requires familiarity with the technique.

Since inflammation is one of the basic hallmarks of atherosclerosis, and the monocytes are a major component of the inflammatory processes during atherosclerosis, monocyte to high-density lipoprotein cholesterol (HDL) ratio (MHR) –which is associated with inflammation– has recently been investigated in subjects with atherosclerotic cardiovascular disease (7, 8). However, the role of MHR in the prediction of subclinical atherosclerosis has not been studied yet. Given the strong association between the inflammatory state and MHR, we hypothesized that MHR would be higher in subjects with subclinical atherosclerosis.

The present study aimed to compare MHR values in subjects with and without increased carotid IMT and determine whether increased MHR would predict increased carotid IMT.

MATERIAL AND METHOD

Study Design

All consecutive subjects aged between 30 and 60 years admitted to our institute's cardiology outpatient clinic, and between June 2017 and August 2017, were enrolled in this cross-sectional study. Subjects with diabetes mellitus, hypertension, or any structural or functional cardiovascular disease on cardiac examination and screening tests (including electrocardiography and echocardiography) were excluded from the study. To diminish any confounders that might influence monocyte levels, subjects with any hematological, immunological, or inflammatory disease that could result in monocytosis were excluded from the study, as well as patients with malignancies and those receiving corticosteroid therapy. The protocol was approved based on the ethical standards of the Declaration of Helsinki. The permissions and consents required for the study were obtained from the Adıyaman University Biomedical Research Ethics Committee (Approval number = 2017/3-7). Informed consent was obtained from the subjects.

Fasting venous blood samples were obtained, and the following parameters were measured: complete blood count, fasting glucose, urea, creatinine, C-reactive protein, and lipid profile (Olympus AU-640 analyzer, Mishima Olympus Co. Ltd, Shizuoka, Japan). At the Adiyaman University Training and Research Hospital biochemistry laboratory, hematological parameters were studied on the "CELL-DYN 3700 SL analyzer (Abbott Diagnostics, Chicago, U.S.A.)" device. Existing cigarette smoking was defined as >10 cigarettes per day. Body mass index (BMI) was calculated using the standard formula of weight (kg)/ height squared (m2). A detailed medical history of each subject was also recorded. All participants underwent transthoracic echocardiography and carotid intima-media thickness measurement with a commercially available cardiac ultrasound system (Vivid E9, GE Medical Systems, Horten, Norway). The left lateral decubitus pose was used for all patients. All patients were examined in detail using the standard two-dimensional echocardiographic method. The same investigator performed all measurements.

Primary Outcome

Subjects were divided into two groups according to carotid IMT values: Those with a carotid IMT greater than 0.9 mm (increased IMT group) and those with a carotid IMT equal to or lower than 0.9 mm (normal IMT group) (9, 10). The difference in MHR values between the two groups and the relationships between MHR and carotid IMT values were the primary and secondary outcome measures of the study.

Statistical Analysis

All analyses were performed on SPSS version 21 (SPSS Inc., Chicago, IL, USA). The sample was divided into two based on the carotid IMT 0.9 mm. Student t-test was used to analyze the differences in numerical data between groups, and a chi-square test was used to analyze the differences of categorical data. Correlation analysis was performed to evaluate the relationship between carotid IMT and MHR, sociodemographic characteristics, and blood parameters. Logistic regression analysis was applied to measure the effect of age, smoking, BMI, and blood parameters on carotid IMT. ROC curve analysis has used the sensitivity and specificity of MHR for predicting carotid artery IMT. The values less than 0.05 were accepted to show statistically significant relationships.

RESULT

A total of 200 subjects (mean age 41.7 ± 8.6 years, 49.5% male) were enrolled in this cross-sectional study. Carotid IMT was >0.9 mm in 50 of the participants (mean carotid IMT 0.93 ± 0.1 mm) and was ≤0.9 mm in the remaining 150 participants (mean carotid IMT 0.56 ± 0.1 mm).

Demographic features and laboratory measurements of the study groups are presented in Table 1. Age, BMI, fasting glucose level, active smoking, total and LDL

cholesterol, monocyte count, and platelet count were significantly higher in subjects with increased carotid IMT than normal carotid IMT. The MHR of the subjects with increased carotid IMT was also substantially higher than that of subjects with normal carotid IMT values (16.7 ± 5.7 vs. 12.8 ± 5.5, p<0.001).

As shown in Table 2, correlation analysis revealed that carotid IMT was significantly correlated with MHR (r=0.325, p<0.001), age (r=0.893, p<0.001), monocyte count (r=0.261, p<0.001), fasting glucose (r=0.261, p<0.001), blood urea nitrogen (r=0.184, p<0.001), total cholesterol (r=0.356, p<0.001), LDL cholesterol (r=0.313, p<0.001), triglyceride level (r=0.293, p<0.001), leukocyte count (r=0.185, p=0.009), neutrophil count (r=0.148, p=0.037), lymphocyte count (r=0.153, p=0.037), whereas it was negatively correlated with HDL cholesterol level (r=-0.210, p=0.003).

Logistic regression analysis demonstrated that age (OR: 1.202, 95% CI: 1.126-1.284, p<0.001) and MHR (OR: 1.190, 95% CI: 1.097-1.291, p<0.001) were significant predictors for a carotid IMT of >0.9 mm (Table 3). ROC curve analysis revealed an MHR cut-off value of 13.4 to identify subjects with increased carotid IMT with a sensitivity of 72% and specificity of 60.7% (Figure 1).

Table 1. Sociodemographic and Clinical Variables of the Groups

	Carotid IMT ≤ 0.9 mm (n=150)	Carotid IMT > 0.9 mm (n=50)	p value
Age (year)	38.5 ± 6.6	51.4 ± 6.6	<0.001**
Gender, Female (n, %)	76 (50.7%)	25 (50%)	0.935
Smoking (n, %)	118 (78.7%)	49 (98%)	<0.001**
BMI (kg/m2)	28 ± 4.6	27.8 ± 3.4	0.010*
Carotid IMT (mm)	0.56 ± 0.1	0.93 ± 0.1	<0.001**
Glucose (mg/dL)	72.8 ± 26.4	125.5 ± 35.2	0.003*
BUN (mg/dL)	28 ± 8.7	29.4 ± 7.3	0.161
Creatinine (mg/dL)	0.73 ± 0.16	0.75 ± 0.19	0.156
Total Cholesterol (mg/dL)	180.8 ± 40.7	204.8 ± 42.2	0.002*
HDL Cholesterol (mg/dL)	43.3 ± 9.4	40.7 ± 7.7	0.052
LDL Cholesterol (mg/dL)	105 ± 30.6	122.2 ± 32.3	0.001*
Triglyceride (mg/dL)	157.8 ± 88.3	192.6 ± 115.4	0.060
WBC (/mm3)	8459.9 ± 1968.5	8948.3 ± 1740.3	0.069
Hemoglobin (g/dL)	15.7 ± 8.9	15.8 ± 11.7	0.289
Neutrophil Count (/mm3)	4891.6 ± 1574.1	5074.8 ± 1393.6	0.337
Lymphocyte Count (/mm3)	2637.9 ± 777	2886.8 ± 944.7	0.138
Monocyte Count (/mm3)	525.6 ± 187.4	657.6 ± 185.8	<0.001**
Platelet Count (x103/mm3)	251.2 ± 124.8	277.3 ± 92.1	0.133
MHR	12.8 ± 5.5	16.7 ± 5.7	<0.001**
CRP (mg/L)	0.43 ± 0.43	0.75 ± 0.19	0.014

Table 2. Correlations Between Carotid Artery IMT Value and Selected Variables

	Carotid IMT	
	r	p
MHR	0.325	<0.001**
HDL Cholesterol	-0.210	0.003*
Monocyte Count	0.261	<0.001**
Age	0.893	<0.001**
Gender	0.096	0.175
BMI	0.129	0.070
Smoking	-0.127	0.073
Fasting Glucose	0.261	<0.001**
BUN	0.184	0.009*
Creatinine	0.070	0.325
CRP	0.035	0.620
Total Cholesterol	0.356	<0.001**
LDL Cholesterol	0.313	<0.001**
Triglyceride	0.293	<0.001**
Leukocyte Count	0.185	0.009*
Hemoglobin	-0.012	0.871
Neutrophil Count	0.148	0.037*
Lymphocyte Count	0.153	0.030*
Platelet Count	0.037	0.601

Table 3. Logistic Regression Analysis Demonstrating the Predictors of Increased Carotid IMT

	Odds ratio	95% Confidence Interval	p value
Age	1.202	1.126-1.284	<0.001**
BMI	0.993	0.875-1.128	0.920
Smoking	0.083	0.051-1.202	0.083
Glucose	1.001	0.995-1.008	0.750
BUN	0.987	0.937-1.039	0.611
Total Cholesterol	1.010	0.986-1.034	0.415
LDL Cholesterol	0.987	0.963-1.012	0.316
Triglyceride	0.966	0.990-1.002	0.235
MHR	1.190	1.097-1.291	<0.001**

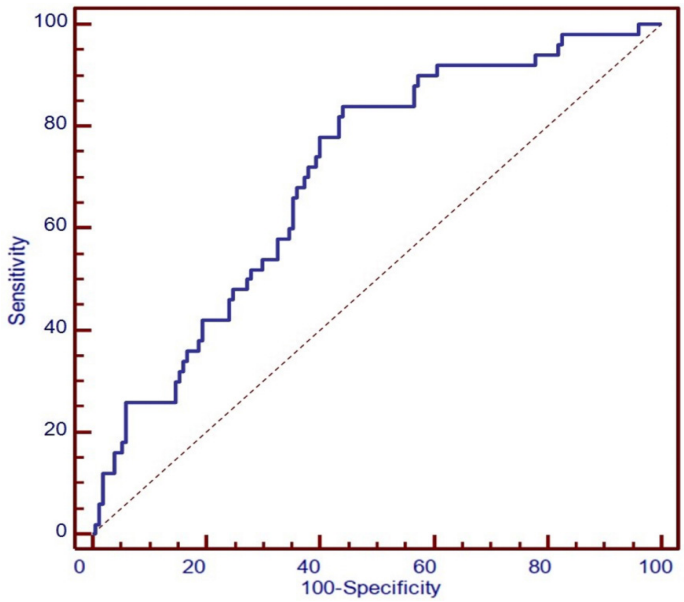

Figure 1. ROC Curve Demonstrating the Sensitivity and Specificity of Monocyte to HDL Ratio for Predicting Carotid Artery Intima Media Thickness

DISCUSSION

Results of the present study demonstrate that MHR is significantly higher in subjects with increased carotid IMT. In addition to the significant correlation between MHR and carotid IMT, MHR was an independent predictor of increased carotid IMT. Moreover, MHR can identify subjects with increased carotid IMT with relatively high sensitivity even though specificity was moderate. These results are promising, particularly when considering that they were obtained from a consecutively enrolled patient group that did not include those with known heart diseases.

Currently, CAD is accepted as a multifactorial disease, and the healing response to vascular injury is considered to allow the initiation and progression of the atherosclerotic plaque (9-11). The presence of hypercholesterolemia is the primary trigger for the initiation of atherosclerosis. In the next step, monocytes adhere to the vascular endothelium and migrate through mechanisms that involve VCAM-1 and selectins. Oxidation of the LDL promotes the secretion of the macrophage chemotactic protein 1. Monocytes change into macrophages within the arterial intima and express scavenger receptors, thus converting into foamy macrophages, which play a critical role in the occurrence and development of atherosclerosis (12). Beyond their activity inside the arterial wall, several immune stimulatory agents and cytokines presenting in blood circulation affect the circulating monocytes and, therefore, contribute to the pathogenesis of CAD and its complications (13). In this briefly explained the complex process, inflammatory activity is likely responsible for plaque instability which may promote plaque rupture, fissuring, or erosion; thus, resulting in the acute presentations of CAD such as unstable angına (14).

High-density lipoprotein, which has been acknowledged as an anti-atherosclerotic lipoprotein under normal physiological conditions, neutralizes the atherosclerotic role of the monocytes. Also, HDL provides various anti-atherosclerotic properties, independent from the monocyte-blocking functions (15-19). The atherosclerotic functions of the monocytes and monocyte-blocking properties possessed by HDL have led to the suggestion that MHR could be a valuable indicator of atherosclerosis. Tani et al. have demonstrated in an intravascular ultrasound study of 114 patients with established CAD that treatment with 40 mg pravastatin leads to a significant reduction in plaque volume and monocyte count in addition to a significant increase in HDL cholesterol level. Multivariate analyses revealed that the rise in serum HDL cholesterol and decreased monocyte count were independent predictors of plaque regression (19). Kundi et al. (20) have shown in 428 patients with stable CAD that MHR was significantly higher in patients with high Syntax scores (≥ 23) and that an MHR value >24 was predictive for a high Syntax score with a sensitivity of 66% and a specificity of 65.1%. Two studies conducted by Akboga et al. have reported that MHR could independently predict CAD as indicated by the high (≥ 23) Syntax score and saphenous vein graft stenosis of >50% (21, 22). Several studies also demonstrate the association between an increased MHR and stent thrombosis, stent restenosis, and no-reflow phenomenon after PCI of the infarct-related artery, in-hospital MACE, and even with in-hospital mortality and long-term mortality (23-26).

This study is the first to report the predictive role of MHR on carotid IMT. Our findings demonstrate that MHR value is significantly correlated with carotid CIMT and that an MHR value of >13.4 was predictive for increased carotid IMT (≥0.9 mm). Given its correlation with carotid IMT and its role in identifying increased carotid IMT, we suggest that the calculation of MHR can be used as a simple, cost-effective, and highly predictive marker of subclinical atherosclerosis. Combining MHR with carotid IMT in subjects with established CAD will probably increase the carotid IMT in predicting the early stages of atherosclerosis. Further studies are required to address the usefulness of the combination of MHR and carotid IMT in detecting subclinical atherosclerosis.

This study also has some limitations to be mentioned. Although we suggest that MHR values are predictive for the presence of subclinical atherosclerosis, this suggestion arises from the assumption that carotid IMT is a robust predictor for the early stages of atherosclerosis. However, the golden standard for detecting atherosclerosis is coronary angiography; however, the study population included in this study did not have CAD established by coronary angiography. Although this is a limitation concerning its usefulness in evaluating the degree of CAD and relationships with other parameters associated with CAD, it is also an advantage in determining its efficacy in previously healthy populations. Additionally, increased carotid IMT is currently accepted as an indicator of

endothelial dysfunction and early atherosclerosis; therefore, the correlation between MHR values and increased carotid IMT is very likely an indication of the presence of subclinical atherosclerosis.

CONCLUSION

The Monocyte-to-HDL ratio is significantly correlated with carotid IMT values. MHR also appears as an independent predictor of increased carotid IMT. We suggest that MHR can be used as a cost-effective and straightforward marker of inflammation for predicting the presence of increased carotid IMT, which is accepted as a reliable indicator of subclinical atherosclerosis.

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Conflict of Interest: *The authors declare that they have no competing interest.*

Ethical approval: *The protocol was approved based on the ethical standards of the Declaration of Helsinki. The permissions and consents required for the study were obtained from the Adıyaman University Biomedical Research Ethics Committee (Approval number = 2017/3-7). Informed consent was obtained from the subjects.*

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