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Original Article

The usefulness of monocyte to high density lipoprotein cholesterol ratio in prediction for coronary artery ectasia

Monosit/yüksek yoğunluklu lipoprotein oranının koroner arter ektaziyi öngörmedeki yararı

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ABSTRACT

Aim: Monocyte count to high density lipoprotein cholesterol ratio (MHR) has been shown to be a useful inflammatory marker in patients with coronary artery disease. Hence, the aim of the study was to evaluate whether there is an association between coronary artery ectasia (CAE) and MHR.

Material and methods: In this retrospective case-control study, a total of 5500 patients who underwent an elective coronary angiography between July 2013 and July 2016 were retrospectively screened. Of these patients, 150 (2.7%) patients were found to have an isolated CAE. The control group was consisted of 150 normal coronary artery patients who matched with this group in terms of age, gender, and body mass index.

Results: The median value of MHR was found to be a statistically higher in patients with CAE ($p<0.05$). In multivariable analyses, MHR (OR: 1.71, 95% CI: 1.219-2.484, $p=0.002$) was found to be an independent predictor of CAE.

Conclusion: We observed that MHR levels were higher in CAE patients when compared to healthy subjects. Our findings may indicate a common pathophysiological mechanism between CAE and coronary artery disease.

Keywords: MHR; inflammation; coronary artery ectasy

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ÖZ

Amaç: Monosit sayısının yüksek yoğunluklu lipoprotein kolesterole oranı (MYYLKO) koroner arter hastalığı olan hastalarda yararlı bir enflamasyon belirteci olduğu gösterilmiştir. Bu nedenle, çalışmamızdaki amacımız MYYLKO'nın koroner arter ektazi (KAE) arasında ilişki olup olmadığını araştırmaktı.

Gereç ve yöntemler: Geriye dönük vaka-kontrol çalışmasında, Temmuz 2013 ve Temmuz 2016 tarihleri arasında elektif koroner anjiyografi olan toplam 5500 hasta tarandı. Bu hastalardan, 150 (2,7%) hastada KAE bulundu. Kontrol grubu yaş, cinsiyet ve vücut kitle indeksi açısından eşleşen 150 normal koroner arter hastalarından oluştu.

Bulgular: MYYLKO'nın ortanca değeri istatistiksel olarak KAE hastalarında daha yüksek bulundu ($p<0.05$).Çoklu değişken analizde, MYYLKO (Odds oranı:1.71, 95%Güven Aralığı:1.219-2.484, $p=0.002$) KAE'nin bağımsız öngörücüsü olarak saptandı.

Sonuç: MYYLKO'nın KAE'li hastalarda sağlıklı kişilere göre daha yüksek olduğunu gözlemledik. Bu bulgularımız KAE ile koroner arter hastalığının ortak bir patofizyolojik mekanizmayı işaret edebilir.

Anahtar kelimeler: MYYLKO; enflamasyon; koroner arter ektazi

Introduction

Coronary artery ectasia (CAE) is described as 1.5 or more times greater dilatation of the normal coronary artery [1]. The involvement of the coronary artery in CAE may be diffuse or focal [1]. In addition, CAE might be found in patient with an obstructive coronary artery disease. Several previous studies reported that the incidence of CAE during elective coronary angiography may range from 0.3 to 4.9% [2-4]. The main underlying mechanism that is responsible for ectasia formation has not been clearly described yet; however, previous studies reported that CAE may be an another form of atherosclerosis. Also, it has been found that the inflammation within the CAE vessel is more potent compared to the normal vessel [5, 6].

In recent years, there has been an increasing interest in describing a simple inflammatory marker in order to facilitate early recognition of patients who may have an increasing risk for future cardiovascular disease. In a recent study, monocyte count to HDL-C ratio (MHR) has been shown as a novel marker of inflammation to predict coronary artery disease severity and future major cardiovascular adverse events in patients with acute coronary syndrome [7]. As the inflammation plays a significant role for the development of CAE, we hypothesized that there may be a relation between MHR and CAE. Hence, in the present study, we aimed to evaluate the potential utility of MHR in predicting CAE.

Material and methods

Study population

In this retrospective case-control study, a total of 5500 patients who underwent an elective coronary angiography between July 2013 and July 2016 in our tertiary heart center due to a presume diagnosis of coronary artery disease were screened. The patients who had an acute coronary syndrome, acute or chronic infection, had use of any glucocorticoid treatment within in three months, had a hematologic and auto-immune disease, undergoing chronic peritoneal dialysis or hemodialysis treatment were excluded from the study. In addition, the patients who had a diagnosis of previous myocardial infarction and patients with liver and gallbladder diseases were excluded from the study. After evaluation regarding with exclusion criteria, 150 (2.7%) patients were found to have an isolated CAE. Also, CAE patients who had non-obstructive coronary artery disease were also excluded from the study. The control group was consisted of 150 angiographically normal coronary artery patients who matched with this group in terms of age, gender, and body mass index. Baseline demographic characteristics and related clinical information were retrieved from the hospital's electronic database. Our local ethics committee approved the study protocol in accordance with the principle of the Declaration of Helsinki. An informed consent was waived because this study had a retrospective design.

Laboratory analysis

In the present study, a complete blood count and biochemical profile was obtained after an overnight fasting in all subjects. The tubes with EDTA were used for automatic blood count. The blood counts were measured using a Sysmex XT-1800i Hematology Analyzer device (Sysmex Corporation, Kobe, Japan). MHR was calculated as the ratio of the number of monocyte to HDL-C and the neutrophil to lymphocyte ratio (NLR) was calculated as the ratio of the number of neutrophil to lymphocytes, both of which obtained from the same blood samples. In our laboratory, the reference value for monocyte count was 2% to 10% of total white blood cells. The C-reactive protein (CRP) level was measured using an automatic biochemical analyzer (Roche Diagonistics Cobas 8000 c502).

Coronary angiography

In the current study, the patients who accepted as having typical angina or with a suspected or positive finding in one of the non-invasive methods that is performed for detection of coronary ischemia underwent an elective coronary angiography. Coronary angiography was performed via femoral or radial artery according to Judkins's technique. All coronary angiograms were recorded into DICOM digital media with a rate of 25 frames/msc. All coronary angiograms were evaluated by two experienced interventional cardiologists who were blinded to patient's clinical data.

Definitions

The CAE was defined as proposed in a previous study [8]. Hypertension was defined as a systolic blood pressure of 140 mmHg or higher, diastolic blood pressure of 90 mm or higher or using an antihypertensive medicine [9]. The presence of diabetes mellitus was accepted as fasting blood glucose of ≥126 mg/dL or higher or currently using an antidiabetic treatment or being on a diet [10]. Local ethics committee approved the study and informed consent was obtained from participant(s)

Statistical analysis

The data was expressed as percentage (%) and median (range: minimum-maximum) values, where appropriate. The Fisher's exact test and Pearson chi-square analysis performed for categorical variables. Fitness to normal distribution was analyzed with the Kolmogorov-Simirnov test. Mann-Whitney-U test was used for comparing quantitative variables with abnormal distribution. The independent risk factors for CAE were analyzed using a multivariate logistic regression analyses with variables that showed statistically significant associations with CAE in the univariate analyses. Statistical analysis was made using the computer software Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 21.0. released 2012, IBM Corp., Armonk, New York, USA). A p-value < 0.05 was considered statistically significant.

Results

In the present study, 150 CAE patients and 150 age-sex-body mass index-matched control subjects constituted the study population. Baseline demographic characteristics and laboratory findings of all patients are shown in Table 1. The frequency of hypertension, diabetes mellitus, and smoking did not reach a statistical significance between the groups (p>0.05 for each). In terms of laboratory findings, there were significant differences between two groups for white blood cell count, monocyte count, lymphocyte count, and creatinine levels (p<0.05 for each). The median value of NLR and MHR were found to be a statistically higher in patients with CAE (p<0.05 for each).

Table 1 Demographic characteristics and laboratory findings of control and study groups

	Control group	CAE presence group	P value
Age, years	55 (40-78)	56 (42-79)	0.124
Gender (female), (%)	80 (53.3)	89 (59.3)	0.295
BMI, kg/m2	25.0 (23.0-27.5)	25.8 (22.0-28.0)	0.252
Hypertension, (%)	80 (53.3)	86 (57.3)	0.486
Diabetes mellitus, (%)	60.7 (91)	58.0 (87)	0.638
Smoking, (%)	62 (41.3)	49 (32.7)	0.120
White blood cell count, 109/µL	7500 (4400-12400)	8400 (4500-10700)	0.004*
Hemoglobin, g/L	140 (108-160)	140 (100-163)	0.631
Monocyte count, 109/µL	400 (0.0-920)	600 (0.0-1500)	<0.001*
Lymphocyte count, 109/µL	1400 (1000-3500)	1300 (700-2500)	0.005*
Neutrophil count, 109/µL	4950 (2160-8680)	5040 (2600-3960)	0.200
Platelet count, 109/µL	288500 (145000-652000)	287000 (198000-652000)	0.997
RDW, %	15.2 (12.2-21.2)	15.3 (12.2-21.2)	0.055
MPV, fL	9.6 (7.9-13.5)	9.6 (7.8-13.5)	0.536
AST, U/L	15 (1-35)	15 (1-35)	0.457
ALT, U/L	15 (2-35)	15 (1-35)	0.400
Creatinine, mg/dL	0.8 (0.5-1.2)	0.9 (0.5-1.5)	0.032*
Total cholesterol, mg/dL	188 (164-226)	195 (165-230)	0.078
LDL cholesterol, mg/dL	125 (20-178)	130 (75-180)	0.363
HDL cholesterol, mg/dL	39 (32-59)	39 (34-55)	0.978
C-reactive protein, mg/L	10 (5-50)	9 (1-50)	0.466
NLR	2.9 (1.8-5.0)	3.5 (2.0-6.4)	0.004*
MHR	9 (1-14)	14 (1-32)	<0.001*

*p<0.05, Continuous variables are presented with median, nominal variables are presented with frequency.
Abbreviations: CAE: coronary artery ectasia, BMI: body mass index, RDW: red cell distribution width, MPV: mean platelet volume, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDL: low density lipoprotein, HDL: high density lipoprotein, MHR: monocyte high density lipoprotein ratio, NLR: neutrophil lymphocyte ratio.

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In univariate analysis, age, white blood cell, NLR, MHR, monocyte and lymphocyte count were found to be related with CAE (Table 2). In order to identify the independent predictors of CAE, multivariate logistic regression analyses with a stepwise backward model was performed using variables that showed marginal association with CAE in the univariate analyses. In multivariate analyses, only MHR (OR: 1.71, 95% CI: 1.219-2.484, p=0.002) was found to be an independent predictor of CAE. A box plot was drawn to show the difference between the MHR and NLR values of control subjects and CAE patients (Figure 1-2).

Table 2 Univariate and multivariate logistic regression analysis giving information about the independent risk factors for CAE

	Univariate analysis			Multivariate analysis		
	95% CI		P value	95% CI		P value
	Lower	Upper		Lower	Upper	
Age	1.000	1.059	0.048	0.983	1.052	0.324
Gender	0.808	2.017	0.295	-	-	-
BMI	0.932	1.316	0.246	-	-	-
Hypertension	0.539	1.341	0.486	-	-	-
Diabetes mellitus	0.704	1.771	0.638	-	-	-
Smoking	0.907	2.326	0.121	-	-	-
White blood cell count	1.029	1.445	0.022	0.727	1.609	0.698
NLR	1.259	1.993	<0.001	0.604	1.919	0.803
MHR	8.693	2.946	<0.001	1.219	2.484	0.002*
Creatinine	0.679	1.418	0.918	-	-	-
Hemoglobin	0.958	1.170	0.263	-	-	-
C-reactive protein	0.764	1.203	0.716	-	-	-
Monocyte count	1.954	8.848	<0.001	0.001	1.640	0.086
Lymphocyte count	0.269	0.823	0.008	0.106	2.371	0.383
Neutrophil count	0.924	1.423	0.215	-	-	-
Platelet count	0.996	1.004	0.991	-	-	-
RDW	0.969	1.239	0.147	-	-	-
MPV	0.979	1.042	0.548	-		
AST	0.955	1.023	0.500	-	-	-
ALT	0.980	1.056	0.371	-	-	-
Total cholesterol	1.000	1.023	0.046	0.999	1.026	0.077
HDL cholesterol	0.949	1.037	0.725	-	-	-
LDL cholesterol	0.987	1.005	0.354	-	-	-

*p<0.05, All clinically relevant parameters were included in the model.
Abbreviations: CAE: coronary artery ectasia, BMI: body mass index, RDW: red cell distribution width, MPV: mean platelet volume, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDL: low density lipoprotein, HDL: high density lipoprotein, MHR: monocyte high density lipoprotein ratio, NLR: neutrophil lymphocyte ratio.

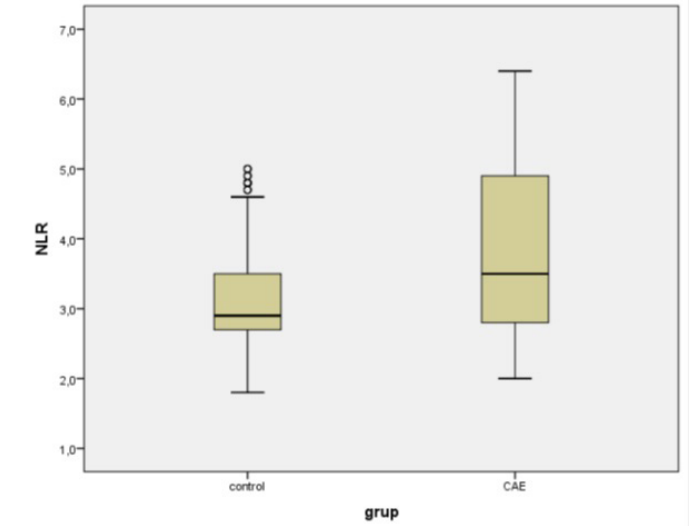

Figure 1: A box plot showing the difference between NLR values of control subjects and CAE patients
Abbreviations: NLR: neutrophil to lymphocyte ratio, MHR: monocyte count to high density lipoprotein cholesterol ratio, CAE: coronary artery ectasia.

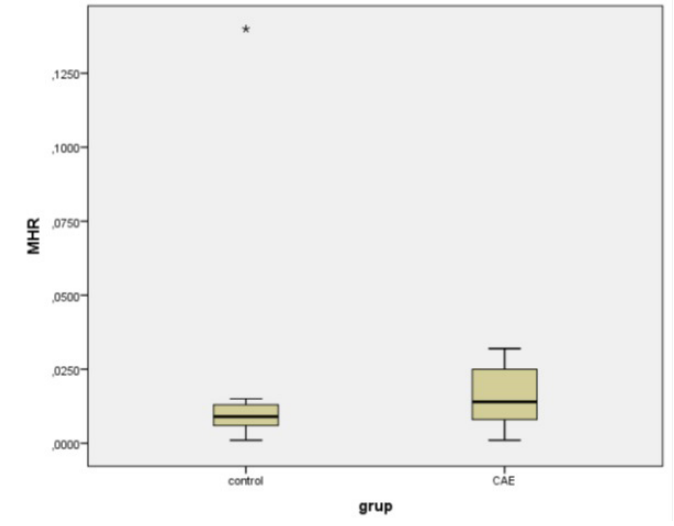

Figure 2: A box plot showing the difference between MHR values of control subjects and CAE patients
Abbreviations: NLR: neutrophil to lymphocyte ratio, MHR: monocyte count to high density lipoprotein cholesterol ratio, CAE: coronary artery ectasia.

Discussion

In the present study, we observed that an elevated MHR may be an independent predictor of CAE. As a simple and easily obtained hematologic parameter from complete blood count, MHR may be used in predicting risk of CAE.

Previously, the inflammatory markers such as CRP, interleukin-6, and vascular adhesion molecules were investigated in patients with CEA [11]. A recent study done by Li and colleagues has shown that interleukin-6 and CRP were significantly higher in patients with CAE when compared to patients with normal coronary arteries [12]. In contrast to this reported previous study, in our study, there was no a significant difference of CRP levels between the groups. This finding may be due to patient-related selection or the size of study sample. Furthermore, plasma soluble intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, and E-selectin levels were found to be higher in patients with CAE than in patients with normal coronary arteries [13]. The NLR, which is also a marker of inflammation, has been investigated in patients with CAE. In a recent published study which constituted of 85 CAE patients, a possible association between NLR and the presence of CAE was examined [14]. The authors found that an increased NLR is an independent predictor of the presence of CAE. Similarly, in our study, we observed a notable increase of median NLR in CAE patients. However, the NLR did not reach a statistical significance in multivariate analysis in our study.

Monocytes secrete several cytokines which may affect platelets and endothelial cells resulting in the stimulation of the proinflammatory and prothrombotic pathways in the human body [15]. During atherosclerosis process, monocytes migrate into subendothelial area and differentiate into macrophages, in which there release some metalloproteinases such as elastase and collagenase [16]. Several previously published studies demonstrated that the differentiation of monocytes into macrophages is the first step in the beginning of atherosclerosis [15, 17]. In contrast to monocyte inflammatory effects, HDL-C has an anti-inflammatory, anti-oxidant as well as anti-platelet effect via several pathways in the human body [16]. These anti-inflammatory and anti-oxidant pathways may include a contribution to the cholesterol outflow from macrophages, inhibition of endothelial adhesion protein expression, and encouraging reverse transport of oxidized molecules [15-17]. Moreover, HDL-C may decrease the inflammation via inhibiting the activation of monocyte and interrupting the differentiation of monocytes to macrophages [18]. Consequently, we thought that a combination of HDL-C and monocyte counts in a single parameter, namely MHR, may better represent the inflammatory process in the human body.

The importance of MHR in cardiovascular disease has been investigated in a few studies. Canpolat et al. investigated the pre-procedural MHR for the prediction of atrial fibrillation recurrence after cryoballoon-based catheter ablation [19]. This study finding demonstrated that an increased MHR was related with an increased recurrence of atrial fibrillation after cryoballoon-based catheter ablation. In addition, it has been shown that MHR may be used to predict coronary artery disease severity [7]. Moreover, in a recent study which consisted of patients with CAE, obstructive coronary artery disease, and normal coronary artery, Kundi et al. reported that high MHR is an independent predictor of CAE and obstructive coronary artery disease [20]. In our study, we also found similar results. However, CAE patients that had non-obstructive coronary artery disease, which was not obvious in the aforementioned study, were not enrolled in our study.

Our results provided evidence that the inflammatory process caused by high MHR levels may cause a microvascular dysfunction in CAE patients. The MHR is a simple and inexpensive marker of inflammation and, it can be calculated easily from complete blood count parameters. An elevated MHR, which is a newly introduced inflammatory marker, may have a predictive value for the prediction of CAE in daily clinical practice.

Study Limitations

This study had some limitations. First, our study had a retrospective design. Second, we were not able to evaluate the plaque burden because patients without evidence of luminal narrowing by angiography may also have plaque burden in the wall of the coronary vessels. Third, by using a spot laboratory value rather than values at a time interval may be another limitation because the development of CAE is a chronic condition. Finally, we did not evaluate other well-known inflammatory markers such as fibrinogen in the study.

Conclusion

We observed that MHR levels were higher in CAE patients when compared to healthy subjects. Our findings may indicate a common pathophysiological mechanism between CAE and coronary artery disease. Finally, our findings warrant further studies to describe a clear role of this marker.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

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