∎Original Article

Monocyte to high-density lipoprotein ratio and high sensitive c-reactive protein levels in patients with isolated coronary artery ectasia

Monosit yüksek/ dansiteli lipoprotein oranı ve yüksek sensiviteli c- reaktif protein değelerinin izole koroner arter ektazisi ile ilişkisi

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Abstract

Aim: Isolated coronary artery ectasia (ICAE) is a rare form of coronary artery disease and has almost same mortality and morbidity rate to atherosclerotic coronary artery disease. Monocyte to HDL-cholesterol ratio (MHR) has been entered the literature as a new inflammatory indicator in various cardiovascular disease. In this study we want to investigate relationship between inflammatory and oxidative markers that high sensitive C reactive protein (Hs-Crp), MHR and ICAE.

Material and Methods: We retrospectively observed patients who underwent elective coronary angiography. Patients with ICAE and normal coronary arteries included in the study. MHR and Hs-Crp levels were observed just before the coronary angiography procedure.

Results: A total of 98 patients (61, 62 % men) patients were included in this study and 28 (28.6%) of them had DM. 68 (69.3%) of patients had ICAE. MHR was significantly higher in patients with ICAE (0.0153 (0.007-0.130)ve 0.0111 (0.005-0.020), p< 0.001). Hs-Crp was also significantly higher in patients with ICAE (Yd-Crp: 6 (0.2-33)ve 1(0.2-14), p < 0.001). MHR was also significantly correlated with Hs-crp levels (r:0,338, p: 0.001). Additionally; DM, smoking, HT, MHR and Hs-crp were detected as independent risk factors of ICAE in logistic regression analysis. In receiver operating characteristic curve analysis, the area under the curve for predicting CAE was 0.744 (p<0,001, 95% confidence interval [CI] 0.64 to 0.84) and cut- off value was 0.013 (sensitivity 69.1%, specificity 63.3%,) for the number of MHR.

Conclusion: MHO and Hs-Crp are markers of inflammation that can be easily and inexpensively examined and found high in patients with ICAE. These markers may be useful explaining the pathogenesis of ICAE and guiding treatment.

Keywords: coronary ectasia; monocyte to high-density lipoprotein ratio; high sensitive c reactive protein

Öz

Amaç: Izole koroner arter ektazisi (İKAE), koroner arter hastalığının az görülen bir formu olup, aterosklerotik koroner arter hastalığna benzer mortalite ve morbidite oranına sahiptir. Monosit yüksek dansiteli lipoprotein (HDL) oranı (MHO) klinikte yeni tanımlanan inflamasyon belirteçlerinden biridir. Çalışamızda MHO ve klinikte inflamasyon belirteci olarak sıkça kullanılan yüksek duyarlıklı C-reaktif protein (Yd-Crp) ile İKAE arasıdaki ilişki araştırılmıştır.

Gereç ve Yöntemler: Çalışmamızda retrospektif olarak elektif koroner yapılan hastalar incelenmiştir. Hastaneye başvuruşunda koroner anjiografi hemen öncesinde alınan örneklerden Yd-Crp ve MHO oranı hesaplanmıştır.

Bulgular: Toplam 98 (61, %62 erkek) hasta geriye dönük incelenmiş, 28 (%28.6) hastada Diabetes Mellitus saptamıştır. İKAE hasta sayısı 68 (%69.8) olarak bulunmuştur. MHO ve Yd-Crp ; İKAE grubunda normal koroner arterlere sahip gruba göre anlamlı olarak yüksek saptandı (Sırasıyla; MHO: 0.0153 (0.007-0.130)ve 0.0111 (0.005-0.020), p< 0.001, Yd-Crp: 6 (0.2-33)ve 1(0.2-14), p < 0.001). Ek olarak MHO ile Yd- Crp değeri arasında pozitif korelasyon saptandı (r:0,338, p: 0.001). Ayrıca; hipertansiyon , Diabetes Mellitus, sigara kullanımı, Yd-Crp ve MHO   değerleri İKAE' nin bağımsız risk faktörleri olarak bulundu. ROC analizinde MHO için eğri altında kalan alan 0.744 (p<0,001, 95% [CI] 0.64 - 0.84) ve cut- off değeri 0.013 (%69.1 sensivite , % 63.3 spesifite) saptandı.

Sonuç: Sonuç olarak MHO ve Hs-Crp basit ve ucuz şekilde bakılabilen inflamasyon belirteçleri olup, İKAE hastalarında yüksek saptanmıştır. Bu beliteçler,   İKAE hastalığının patogenezinin aydınlatılmasında ve tedavinin yönlendirilmesinde faydalı olabilir.

Anahtar Kelimeler: koroner arter ektazisi; monosit yüksek dansiteli lipoprotein (hdl) oranı; yüksek duyarlılıklı c- reaktif protein.

Introduction

Isolated coronary artery ectasia (ICAE) is a rare coronary anomaly and commonly accepted to be a different form of coronary artery disease (CAD). ICAE may be asymptomatic in cases without obstructive CAD, but it can show up with coronary ischemia signs.[1] Monocytes are one of important mononuclear cells that develop in the bone marrow and circulate within the bloodstream. Monocytes are special cell types for secretion of inflammatory cytokines. These cells are important during the early stages of atherosclerosis and the local proliferation that is responsible for atherosclerotic progression. Thus, monocytes have an important   role in early stage lesions and in the chronic stages of the disease. [2] Additionally, high-density lipoproteincholesterol (HDL-C) protects endothelial cells against the atherogenic effects of low-density lipoprotein cholesterol (LDL-C) and inflammatory cells. [3-5] This effects reverse atherosclerosis progress. So, HDL-C has very important role in anti-inflammatory actions. Monocyte to HDL-cholesterol ratio (MHR) and High sensitive C- reactive protein (Hs-Crp) are very considerable inflammatory markers and several studies have shown that strong correlation between various cardiovascular diseases.[6-8] Because of inflammation is the main cause of ICAE; increased MHR and Hs-Crp may be associated with pathogenesis of ICAE. In the literature, there is not enough studies about MHR in patients with ICAE. Although the relationship between the risk of developing CAE and MHR was demonstrated [9], there is a relationship between MHR and Hs-Crp in the patient with ICAE is still unclear. Thus, the aim of this study was to assess whether there is a relationship MHR and Hs-Crp in patients with ICAE.

Material and Methods

Study population

Total of 98 consecutive patients with ICAE undergoing coronary angiography were retrospectively enrolled in our study, between February 2014 and December 2017. Patients with cardiopulmonary arrest, active infection, systemic inflammatory disease, contrast medium administration within 15 days, chronic renal failure (serum creatinine >2 mg/dl), end-stage liver disease, malignancy and using lipid-lowering drugs were excluded from the study. We also excluded patients with left ven-tricular ejection fraction [LVEF]<50%, percutaneous coronary intervention and coronary artery bypass grafting history. ICAE   which is not accompanied by a significant coronary artery stenosis described as dilatation of at least one coronary artery so as to be 1.5-fold or greater than the normal coronary artery segment and (1). Diabetes mellitus (DM) was described by fasting serum glucose levels of at least 126 mg/ dl, a random plasma glucose level of >200 mg/dl and/

or if the patient was taking oral anti-diabetic drugs, or insulin. Hypertension (HT) was described as a systolic blood pressure > 130 mmHg and/or a diastolic blood pressure > 80 mmHg or treatment with any antihypertensive drugs. Hyperlipidemia (HL) was described as a total cholesterol greater than 200 mg/dl and/or a low-density lipoprotein cholesterol (LDL) level greater than 130 mg/dl or previously treated HL. Current smokers are described who have smoked regularly in the previous 6 months. A family history of coronary artery disease was defined as a coronary event occurring in men before 55 years old or a coronary event occurring in women before 65 years of age. The hospital local ethics committee approved our study. Our study was performed in accordance with the Helsinki Declaration.

Coronary angiography and intervention

Coronary angiography was performed according to clinical indications (Stress echo, treadmill test, myocardial perfusion scintigraphy or typical chest pain). Coronary angiography (CA) (Siemens Axiom Artis zee 2006; Germany) was performed by femoral or radial approach according to standard practice. We performed echocardiography (Philips Epiq 7, Medical System) to all patients during hospitalization. The left ventricular systolic performance was calculated using the modified Simpson's method.

Laboratory analysis

Complete blood count (CBC) and cholesterol levels were measured at the time of admission. For definition of CIN, serum creatinine levels were measured before and after procedure. CBC levels were observed using Cell-Dyn 3700 (MAPSS Laser Differential; Abbott Laboratories, USA). Cholesterol levels that total cholesterol, HDL-C and triglyceride, were observed enzymatically (Hitachi 7350 autoanalyzer, Hitachi Ltd, Japan). Additionally, LDL-C levels were measured with Friedewald formula. MHR was calculated by dividing monocyte count (109/L) to HDL-C level (mmol/L). The estimated glomerular filtration rate (eGFR) was measured using the Modification of Diet in Renal Disease formula [20]. High-sensitivity C-reactiveprotein (hsCRP) was measured by using Beckman Coulter analyzer before the coronary angiography.

Statistical analysis

Statictical analyses were observed using SPSS version 22.0 package program (SPSS Inc, Chicago, Illinois). Kolmogorov Smirnov testing was used to determine the subjects' distribution. Normally distributed variables are presented as mean ± standard deviation (SD) and not normally disturbed subjects were showed median and quartile range. The independent samples t test was used to compare the values and nonparametric values were compared using the Mann-Whitney U test. Chi-square test were performed for comparison of categorical variables. To evaluate the effects of various factors on ICAE development, regression analyses using the backward Logistic Reggression (LR) method were performed. Variables for which the P value of <0 .05 was considered significant. Receiver operating characteristic (ROC) curve analysis was used to determine the optimum cut-off values to predict the development of ICAE.

Results

A total of 98 patients (61, 62 % men) patients were included in this study and 28 (28.6%) of them had DM. 68 (69.3%) of patients had ICAE. MHR was significantly higher in patients with ICAE (0.017± 0.0014 vs 0.011± 0.003, p: 0.033). Hs-Crp was also significantly higher in patients with CAE (7.2± 4.4 vs 1.6± 2.6, p < 0.001). Weight, age and males were significantly higher in patients with CAE. Also, general risk factors that HL, smoking and HT were significantly higher in patients with ICAE. Previous medications, HbA1c, DM rates were not differed between two groups. The baseline clinical characteristics of patients were shown in Table 1 and 2. MHR was also significantly correlated with Hs-crp levels (r:0,338, p: 0.001). Additionally; DM, smoking, HT, MHR and Hs-crp were detected as independent risk factors of ICAE in logistic regression analysis (Table 3). In ROC curve analysis, the area under the curve for predicting CAE was 0.744 (p<0,001, 95% confidence interval [CI] 0.64 to 0.84) and cut- off value was 0.013 (sensitivity 69.1%, specificity 63.3%,) for the number of MHR (Table 4) (Figure 1).

Table 1. Main Characteristics of Patients

	Patients with CAE (n:68)	Patients without CAE (n:30)	P
Age (year)	63.0± 10.8	54.2± 9.9	<0.001
Men (n%)	48 (70.6%)	13(43.3%)	0.010
BMI (kg/m2)	29.6±5.5	31.9±6.2	0.077^
HT (n%)	52(76.5%)	15 (50.0%)	0.009
HL (n%)	42 (61.8 %)	8 (26.7%)	0.001
DM (n%)	17 (25.0 %)	11(36.7 %)	0.23
Smoker (n%)	39 (57.4%)	9(30.0%)	0.013
EF(n%)	60(20-60)	60(60-60)	<0.001*

HT: Hypertension, DM: Diabetes Mellitus, HL: Hyperlipidemia, EF: Ejection fraction, CABG: Coronary artery bypass grefting, BMI: Body mass index. *: Mann-Whitney U test , ^: Independent samples t test

Table 2. In-hospital clinical course of Patients

	Patients with CAE N: 68	Patients without CAE N:30	p
MHR	0.0153 (0.007-0.130)	0.0111 (0.005-0.020)	<0.001*
WBC	7.7±2.1	7.6±1.9	0.79^
HGB	13.4±1.6	12.8±1.6	0.13^
PLT	250.7±66.7	246.1±82.9	0.77^
NEU	4.8±2.0	5.0±1.9	0.72^
LYM	2.0±0.6	1.8±0.7	0.23^
MON	0.6±0.5	0.6±0.1	0.67^
HDL	37(26-44)	52 (43-63)	<0.001*
LDL	120.4±31.8	120.7±42.2	0.97^
TG	121(46-480)	144(44-437)	0.12*
NON HDL	157.1±34.9	150.2±50.1	0.010^
Glucose (mg/dl)	104 (59-321)	105 (79-284)	0.57*
HBA1C (%)	5.7±0.6	5.5±0.6	0.80^
Creatinine (mg/dl)	0.96 (0.55-2.24)	0.98 (0.57-1.99)	0.89*
Hs-Crp	6 (0.2-33)	1(0.2-14)	<0.001*
Uric Acid	5.6±1.6	6.0±2.5	0.011^

MHR: Monocyte HDL ratio, Hs-Crp: High sensitive Crp, *: Mann-Whitney U test , ^: Independent samples t test

Table 3. Independent risk factors of CAE in logistic regression analysis

Variables	OR (95% C.I)	P
Age	1.1 (0.9-1.3)	0.019
MHR	0.70(0.5-0.9)	0.006
Smoke	0.77(0.60-0.98)	0.038
Hs-Crp	0.9(0.7-1.2)	0.003
Gender	1.6 (0.7-3.8)	0.032
DM	0.6 (0.4-1.3)	0.020
HT	0.6 (0.5-0.8)	0.015

HT: Hypertension, DM: Diabetes Mellitus, BMI: Body mass index , MHR: Monocyte to HDL ratio, Hs-Crp: High sensitive Crp

Table 4. Receiver operating characteristic (ROC) curve analysis

	Area	Std. Error	Asym. Sig.	Confidence interval
MHR	0.744	0.051	<0.001	0.6-0.8

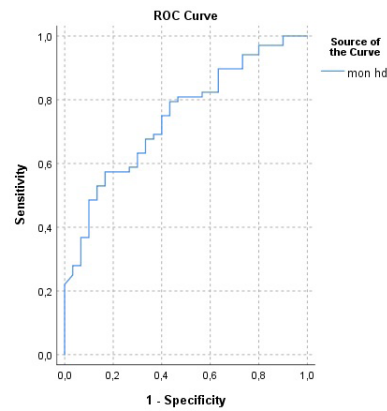MHR: Monocyte to HDL ratio,

Figure 1: Receiver operating characteristic (ROC) curve analysis.

Discussion

ICAE is rare situation that may be congenital or acquired and its common aetiologies are 50% atherosclerosis, 20-30% congenital diseases, and 10-20% inflammatory or connective tissue diseases.[10-12] ICAE is very rare and mostly asymptomatic. Symptomatic cases usually suffer form of effort angina. However, it may also manifest itself with unstable angina. Reduced coronary flow due to microvascular dysfunction has been demonstrated to be responsible for ischemia in cases that have not stenotic CAD. Some publications reported that ectasia caused slow flow, thrombus formation and vasospasm in coronary arteries, also lead to myocardial infarction without obstructive CAD.[12,13] Current studies showed that inflammatory processes has a great role in the aetiopathogenesis of ICAE and also a previous study revealed that damage of the vascular media layer as the cause of this pathology.[14] Therefore, inflammatory cells can be detected in this vascular layers.[15]

Blood cell derived tests are an easy and effective methods to observe the systemic inflammation in various diseases. Recents studies have presented that elevated systemic inflammatory markers have been linked to various cardiovasculary pathologies. Monocyte cell which is a one of leukocyte type have an important role during inflammatory process and its activation plays a key role in cardiovascular diseases.[15,16] The most important cause of atherosclerosis is considered inflammation, so monocytes share in the onset and progression of atherosclerosis.

HDL-C particles block macrophage cell activation and remove cholesterol particles from endothelium.[17] These molecules

provide anti-inflammatory effects. The monocyte chemotaxis reveals an inflammatory and toxic effect, but HDL-C molecules have preventive functions during this pathological process. Therefore, the ratio of two parameters can provide important information about the inflammatory state. MHR is a novel marker that gives important information about inflammation. Although the relationship between the risk of developing CAE and MHR was demonstrated [9], the role of MHR was lessknown during development of ICAE. Therefore, we hypothesized that an increased MHR may explain pathophysiology and be an early predictor of ICAE. Recent studies showed that increased MHR was an independent risk factor of major cardiovascular events in patients with chronic kidney disease and atrial fibrillation recurrence after cryoballoon.[15,16,18-22]. In our study, we observed that patients with ICAE have significantly higher MHR and Hs-Crp levels compared to control group and our findings also indicated that an MHR and Hs- Crp were significantly independent risk factor of ICAE. MHR has a strong positive correlation with serum hs-CRP level, which supports its important role in systemic inflamation. For this results, MHR may gain a critical role for prediction of ICAE during diagnostics follow-up.

Other risk factors that smoking, HT and DM are common in patients with coronary artery disease and comorbid ICAE in previous studies.[11] Our study suggested these results that DM, smoking, HT and Hs-crp were detected as independent risk factors of ICAE.

Our study has several limitations. First, it is retrospective and a single-center study. Second, we used a single MHR value before the procedure. Another limitation is that the visual observation of coronary angiography was only performed. Finally, the number of patients were relatively small and we did not follow- up patients for futher evaluation.

Conclusion

MHO and Hs-Crp are markers of inflammation that can be easily and inexpensively examined and found high in patients with ICAE. These markers may be useful explaining the pathogenesis of ICAE and guiding treatment.

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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