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ORIGINAL ARTICLE

Monocyte High-Density Lipoprotein Cholesterol Ratio and Coronary Collateral Circulation Development in Patients with Stable Coronary Artery Disease and no History of Revascularization

Sinan Varol, Fahrettin Katkat, Serkan Karahan, İrfan Şahin, Ertuğrul Okuyan

Department of Cardiology, Bagcilar Training and Research Hospital, Istanbul, Türkiye

Abstract

Introduction: In patients with chronic total occlusion (CTO), various degrees of coronary collateral circulation (CCC) can be seen. No clinical study was conducted for the relationship between monocyte/high-density lipoprotein cholesterol ratio (MHR) and the development of CCC.

Methods: Among 17,391 patients, the angiographic procedures were analyzed. Patients who had a history of acute coronary syndrome, myocardial infarction, percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) procedure were excluded from the study. A total of 217 patients with CTO were retrospectively analyzed. The Cohen-Rentrop classification was used for retrograde CCC score.

Results: Both patient groups were male dominant. The prevalence of hypertension and diabetes was similar. MHR values did not differ between poor CCC versus good CCC groups (13.90±6.34 vs. 14.33±7.57, respectively, p=0.948). About 15.5% of patients in the poor CCC group and 19.9% of patients in the good CCC group have multiple CTOs.

Discussion and Conclusion: MHR as a novel marker of inflammation and atherosclerotic index is not related to CCC development in patients with CTO and stable coronary artery disease.

Keywords: Collateral circulation; coronary arteries; high-density lipoprotein cholesterol; monocyte; ratio.

Coronary collateral circulation (CCC) can develop as a response to chronic myocardial ischemia[1]. These structures exist in newborn and supply oxygen support for jeopardized myocardium[2]. In patients with chronic total occlusion (CTO), various degrees of CCC can be seen. Sufficient CCC has a preventive effect in myocardial infarction, fatal arrhythmia, ventricular failure, and ventricular aneurysm formation[3-6]. Besides, chronic inflammation has a negative effect on CCC development,[7,8] and it plays an important role in the initiation and progression to atherosclerosis[8].

The majority of leukocytes in atherosclerotic plaques are macrophages and they are believed to be different from monocytes recruited from circulating blood[9]. Circulating monocyte count is predicted by new plaque development[10]. High-density lipoprotein (HDL) cholesterol is an anti-atherogenic molecule and effects mainly with reverse cholesterol transport[11]. It also inhibits the migration of

Correspondence (İletişim): Sinan Varol, M.D. Bağcılar Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, İstanbul, Türkiye
Phone (Telefon): +90 555 622 34 10 **E-mail (E-posta):** sinanvarol@gmail.com
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macrophages to atherosclerotic plaque. Monocyte/HDL cholesterol ratio (MHR) has been associated with the severity of coronary atherosclerosis and cardiac events[10,12,13]. No clinical study was conducted between MHR and the development of CCC.

Materials and Methods

Patient Population

Patients who have stable angina and underwent coronary angiography between May 2009 and December 2015 were retrospectively analyzed based on hospital records. Among 17,391 angiographic procedure, patients who had a history of acute coronary syndrome, myocardial infarction, percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) procedure, heart failure (ejection fraction (EF%) < 40%), malignancy, severe valvular heart disease, hematological diseases which affect leukocyte count, acute/chronic infective, or inflammatory disease were excluded from the study. A total of 217 patients who have one or more major artery CTO were included in the study. CTOs were considered to be total occlusion with a duration longer than 3 months of evidence by prior angiogram or onset of symptoms. The clinical risk factors of the patients, such as age, gender, hypertension, and diabetes, were noted. Patients receiving antihypertensive therapy or with arterial blood pressure above 140 mmHg for systolic and/or 90 mmHg for diastolic were considered to be hypertensive. Diabetes mellitus was defined as the use of antidiabetic drugs or a fasting blood glucose level above 126 mg/dL. Total cholesterol >200 mg/dL, LDL cholesterol >130 mg/dL, and receiving lipid-lowering drugs were defined as hyperlipidemia. Blood samples were taken on admission. Hematologic parameters were performed by an automatic blood counter (A Sysmex XE-2100, Sysmex, Kobe, Japan). Serum creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lipid profile were measured using an auto-analyzer (Roche Diagnostic Modular Systems, Tokyo, Japan). MHR values were calculated. Transthoracic echocardiography was performed by experienced cardiologists before patient discharge. Philips iE33 Ultrasound system with 3.5 MHz echocardiography probe (Philips Healthcare, The United States) was used.

Coronary Angiography

Selective coronary angiograms were performed through the femoral artery using the Seldinger technique. CCC was assessed by two experienced interventional cardiologists retrospectively. Any differences in the assessment were resolved by a third interventional cardiologist who was blinded to the results of the first two reviewers. The Cohen-Rentrop classification was used for retrograde CCC scores. According to this method, Grade 0: No filling of any collateral vessels; Grade 1, filling of side branches of the artery to be perfused by collateral vessels without visualization of the epicardial segment; Grade 2, partial filling of the epicardial artery by collateral vessels; and Grade 3, complete filling of the epicardial artery by collateral vessels[14]. Thrombolysis in myocardial infarction (TIMI) flow score was used for the assessment of anterograde collateral circulation score and calculated as follows: Grade 0, no filling any collateral vessels; Grade 1 partial filling of the epicardial artery by collateral vessels; Grade 2 complete but very slow filling of the epicardial artery by a collateral vessel; and Grade 3, complete visualization and rapid filling of the epicardial vessel.

Patients who have a TIMI flow (anterograde) score above 1 were excluded from the study. Rentrop (retrograde) score was used for CCC assessment. Patients with Grades 0–1 filling were considered as poor CCC group. Patients with Grades 2–3 filling were classified as good CCC group. In patients with multiple CTOs, the higher Rentrop score was used. Both groups were compared.

The study was approved by our Clinical Research Ethics committee of Bagcilar Training and Research Hospital on August 17, 2017, as a 2017-601 protocol number. The study protocol complied with the Declaration of Helsinki.

Statistical Analysis

Statistical analysis and data presentation were carried out using SPSS 20.0 for Windows (SPSS, IBM Corp.). Descriptive statistics were produced using means, medians, ranges, and standard deviations for continuous variables, and percentages were taken for categorical variables. The Chi-square test or exact Fisher's tests were used to compare percentages. To test the distribution pattern of variables, the Kolmogorov–Smirnov test was used. Continuous variables of normally distributed variables were analyzed with an independent t-test, and continuous variables of non-normally distributed variables were analyzed with the Mann–Whitney U-test. Statistical significance was evaluated at the 5% (α=0.05) level.

Results

A total of 217 patients (169 males [77.9%]; mean age was 62.2±10.1 years) enrolled in the study. The baseline char-

acteristics of the two groups are listed in Table 1. There were 71 patients (54 males [76.1%]; mean age 62.3±10.2 years) in the poor CCC group and 146 patients (115 males [78.8%]; mean age 62.1±10.1 years) in the good CCC group. Age was similar between groups. Both patient groups were male dominant. The prevalence of hypertension and diabetes was similar. There was no difference between hemoglobin, creatinine, CRP, cholesterol, and triglycerides. About 15.5% of patients in the poor CCC group and 19.9% of patients in the good CCC group have multiple CTOs. The highest Rentrop-Cohen score was used in patients with multiple CTOs. Most of the CTOs were localized on RCA. MHR values did not differ between groups. The distribution of patients and MHR values according to Rentrop scores is shown in Figure 1.

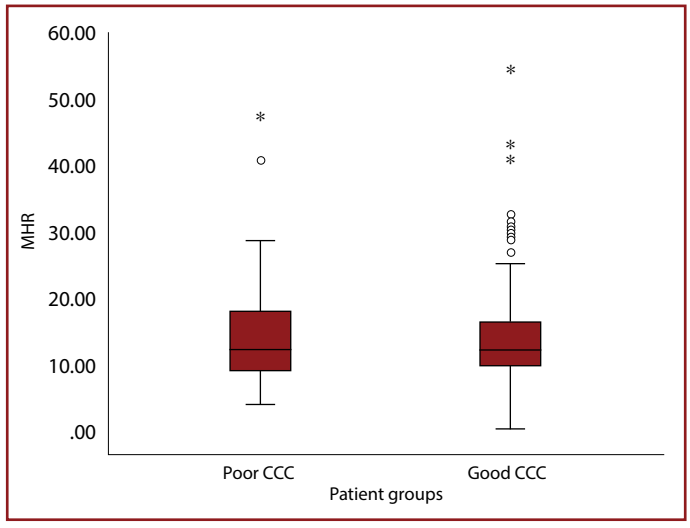

Figure 1. Distribution of monocyte/HDL ratio between groups. No significant difference exists.

Table 1. Properties of patient groups

	Poor CCC (n=71)	Good CCC (n=146)	p
Age	62±10	62±10	0.925
Gender	54 (76.1%) males	115 (78.8%) males	0.652
	17 (23.9%) females	31 (21.2%) females	
Hypertension	66.2%	67.4%	0.860
Diabetes	36.8%	29.6%	0.304
Hyperlipidemia	73.2%	65.8%	0.267
Ejection fraction (EF%)*	60 (50–60)	60 (45–60)	0.349
Hemoglobin (gr/dL)	13.6±1.7	13.7±1.9	0.717
Creatinine (mg/dL)*	0.91 (0.80–1.08)	0.93 (0.86–1.09)	0.484
AST (U/L)*	19.5 (16–26)	20 (17–26)	0.447
ALT (U/L)*	20.5 (14–26)	21 (16–27)	0.392
T. cholesterol (mg/dL)*	195 (174.5–238)	202.6 (173–236)	0.816
HDL (mg/dL)*	43 (38–50.8)	41.7 (35.8–47.6)	0.165
LDL (mg/dL)	123±44	126±38	0.545
Triglyceride (mg/dL)*	167 (120–247)	158 (115–223)	0.618
WBC (10^3/μL)	8.34±2.03	8.07±1.94	0.354
Neutrophil (10^3/μL)	5.14±1.59	5.06±1.64	0.760
Lymphocyte (10^3/μL)	2.28±0.81	2.18±0.86	0.414
Monocyte (/μL)*	550 (420–710)	510 (410–730)	0.536
CRP (mg/dL)*	4.0 (1.9–7.9)	4.6 (1.5–13.5)	0.696
PLT (10^3/mm^3)	257±73	242±69	0.158
MHR*	12.56 (9.22–18.18)	12.12 (9.95–15.96)	0.948
Number of CTO artery	One: 60 (84.5%)	One: 117 (80.1%)	0.720
	Two: 10 (14.1%)	Two: 27 (18.5%)	
	Three: 1 (1.4%)	Three: 2 (%1.4)	
CTO localization	LAD: 30 (42.3%)	LAD: 56 (38.4%)	0.582
	Cx: 12 (16.9%)	Cx: 36 (24.7%)	0.197
	RCA: 41 (57.7%)	RCA: 85 (58.2%)	0.947

*Data given as mean ± standard deviation or %. Data marked with an * (asterisks) given as median and interquartile range. ALT: Alanine aminotransferase, AST: Aspartate transaminase, CCC: Coronary collateral circulation, CRP: C-reactive protein, CTO: Chronic total occlusion, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, MHR: Monocyte/HDL ratio, PLT: Platelet count, WBC: White blood cell.

Discussion

The relationship between CCC and inflammation has been demonstrated. Despite the severity of coronary stenosis, duration of angina has a positive effect for developing CCC and a marked variety of collateral vessel development exists between similar stenosis[14,15]. Increased concentrations of tumor necrosis factor (TNF)-alfa, interleukin-6, soluble adhesion molecules, and high-sensitivity C-reactive protein (hs-CRP) were found to be related to poor CCC[16-20]. Alteration of white blood cells and differentials was associated with the inflammatory condition, and a relationship with cardiovascular disease has been demonstrated[21,22]. Monocytes and macrophages are the most important cell types for the production of pro-oxidant and pro-inflammatory cytokines at the site of inflammation[23]. HDL cholesterol particles have a vasodilatation effect and increase endothelial nitric synthase expression[24,25].

Furthermore, monocytes and HDL cholesterol were important for developing atherosclerosis. During atherosclerotic plaque formation, monocytes from systemic circulation are recruited into the intima and differentiate into foam cells by taking up oxidized LDL and other lipids[26]. HDL cholesterol particles have been shown anti-atherogenic properties by removing cholesterol from macrophages, exhibiting an antioxidant effect[27,28]. MHR shows the atherogenic and anti-atherogenic balance[29].

The relationship between MHR and coronary artery severity was also demonstrated[12,30,31]. MHR is studied in both acute coronary syndromes (ACSs) and stable coronary artery disease. It is associated with TIMI score in ACS,[32] thrombus burden, and no-reflow in ST-elevation myocardial infarction (STEMI),[33,34] in-hospital and long-term mortality in STEMI[35,36]. MHR was found to be higher in bare-metal stent (BMS) restenosis[37-39] and saphenous vein disease in coronary bypass[40].

We hypothesized that MHR may be related to CCC development because of its relationship with atherogenic and inflammatory processes. However, in our study, there was no significant difference between MHR values between good CCC and poor CCC groups. CRP values were also similar. It should be noted that the study population has stable CAD patients with no history of acute coronary syndrome or myocardial infarction, no history of coronary revascularization, and no history of congestive heart failure. These findings also indicate that neither micro-inflammatory tonus nor atherosclerotic risk factors are distinctive factors for CCC development on CTO lesions in "stable" patients. A lot of other factors were also described. Insulin-like growth factor-1 (IGF-1) levels, macrophage migration inhibitory factor, serum endocan, endostatin, and apelin are higher in patients with good CCC[41-45]. Subclinical hypothyroidism is related to poor CCC[46]. In the small studies on subtotal coronary lesions, vascular endothelial growth factor (VEGF), ghrelin, and omentin-1 were found to be high in the good CCC group[47,48].

To the best of our knowledge, the present study is the first investigation into the relationship between MHR and CCC development in patients with CTO.

The major limitation of our study that it is single centered and it has a relatively small number of patients. We aimed to detect the pure effects of MHR. Hence, our study eliminated a lot of patients who had a history of acute coronary syndrome, history of myocardial infarction, history of PCI or CABG, and heart failure with an ejection fraction lower than 40%. Further studies that include these mentioned patient groups could exhibit the effects of MHR and CCC development.

Conclusions

MHR, as a novel marker of inflammation and atherosclerotic index, seems to be not related to CCC development in patients with CTO and stable conditions. A couple of other factors can play a dominant role in this process.

Ethics Committee Approval: The study was approved by our Clinical Research Ethics committee of Bagcilar Training and Research Hospital on August 17, 2017, as a 2017-601 protocol number. The study protocol complied with the Declaration of Helsinki.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: S.V.; Design: S.V.; Data Collection or Processing: S.V., F.K., S.K.; Analysis or Interpretation: S.V., I.S., E.O.; Literature Search: S.V.; Writing: S.V., F.K., S.K.

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