Original Article

The Predictive Value of Serum Monocyte to High-Density Lipoprotein Ratio for Coronary Collateral Circulation in Patients with Stable Coronary Artery Disease

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Abstract

Introduction: Coronary collateral circulation (CCC) is an adaptive response to chronic myocardial ischemia. The monocyte to high-density lipoprotein cholesterol ratio (MHR) has been reported as a new predictor and prognostic indicator of cardiovascular diseases. **Objective:** In this retrospective study, we aimed to investigate the association between MHR and CCC in stable coronary artery disease (CAD). **Materials and Methods:** A total of 355 consecutive patients who were admitted to our hospital for coronary angiography with stable angina pectoris with ≥90% stenosis were enrolled into the study. The CCC was graded using the Rentrop Classification: Grade 0-1–2-3. **Results:** MHR (12.5 ± 4.5 vs. 16.4 ± 5.7, $P < 0.01$) is significantly higher in the well CCC group than in the poor CCC group. We demonstrated that MHR levels are significantly related with the Rentrop classification of CCC. In the Rentrop III group, the MHR value was significantly higher ($P < 0.01$) than the Rentrop-0, Rentrop-I, and Rentrop-II group. In the Rentrop II group, the MHR value was significantly higher ($p<0.01$) than in the group with Rentrop-0 and Rentrop-I. This study showed that, in stable CAD, MHR levels are significantly higher in patients with good CCC than in those with poor CCC. **Conclusion:** MHR may serve as an independent predictor of good CCC in patients with ≥90% coronary stenosis. **Limitations:** This study is subject to the limitations inherent to a retrospective study, and the sample size in our study is relatively small.

Keywords: Coronary collateral circulation, monocyte to high-density lipoprotein ratio, stable coronary artery disease

Introduction

The development of coronary collateral circulation (CCC) is an adaptive response to chronic myocardial ischemia and protecting from the tissue damage and infarction.[1] These vessels provide an alternative source of blood supply to the myocardium in patients with occlusive coronary lesions. Increase in coronary collateral blood flow may reduce anginal symptoms and cardiovascular events and preserve contractile function.[2] The number of collaterals and the extent of their coverage are associated with improved survival in patients with coronary heart disease. There have been numerous studies that show a protective role of well-developed versus poor-developed collateral arteries demonstrating smaller infarcts, less ventricular aneurysm formation, reduction in postinfarct ventricular dilatation, and reduced future cardiovascular events.[3,4] Moreover, finally, it was shown that, in patients with chronic stable coronary artery disease (SCAD), a well-developed CCC might reduce mortality.[5] Patients with coronary artery stenosis or occlusion develop varying degrees of collateral formation despite similar degrees of coronary

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obstruction. Although the severity of coronary stenosis, presence of diabetes mellitus, levels of inflammatory cells, and dyslipidemia, were all suggested as the potential determinants of collateral development, the mechanisms for the different individual ability to develop collateral circulation are still unclear.[4,6-8]

Circulating monocytes as a source of various cytokines and molecules, interact primarily with platelets and endothelial cells leading to the aggravation of inflammatory, pro-thrombotic pathways.[9] On the contrary, high-density lipoprotein cholesterol (HDL-C) counteracts these proinflammatory and pro-oxidant effects of monocytes by hindering the migration of macrophages and oxidation of low-density lipoprotein (LDL) molecules as well as promoting the efflux of cholesterol from these cells.[10] In addition to the HDL-C particles' well-known anti-inflammatory and antioxidant actions, recently, these molecules have been claimed to have a suppressive role in controlling monocyte activations and proliferation-differentiation of the progenitor cells of monocytes.[11,12] As a recently emerged inflammation-based marker, the monocyte count to high-density lipoprotein cholesterol ratio (MHR) has been reported as a new predictor and prognostic indicator of cardiovascular diseases.[13-15]

However, there are no data on the association of these new parameters (MHR) with the CCC. In this retrospective study, we aimed to investigate the association between MHR and CCC in patients with stable CAD.

Materials and Methods

Between January 2012 and December 2016, a total of 355 consecutive patients, who were admitted to our hospital for coronary angiography procedure with stable angina pectoris with ≥90% stenosis, were enrolled to this study and evaluated. All patients had stable anginal symptoms and/or positive stress test or myocardial perfusion scintigraphy results or electrocardiographic/echocardiographic changes indicating myocardial ischemia. Clinical information, including age, sex, body mass index (BMI), history of hypertension and diabetes mellitus, smoking, current medications, complete blood count, serum cholesterol, fasting glucose levels, and left ventricular ejection fraction values, was obtained from a review of the patients' chart. Patients were excluded from the study if they had recent (within 3 months) history of acute coronary syndrome, decompensated heart failure, a recent history of blood transfusion, active and ongoing infection, chronic inflammatory or autoimmune disease, active cancer or hematological proliferative diseases, severe hepatic diseases, renal failure, and history of percutaneous coronary intervention or coronary artery bypass grafting. The study protocol was approved by the Local Ethics Committee. Patient Consent Declaration was obtained from the patients. The study was conducted in accordance with the Helsinki Declaration.

The patients were defined as hypertensive if their blood pressure was 140/90 mm Hg or if the individual was taking any anti-hypertensive medications. Diabetes mellitus was defined as the presence of a history of antidiabetic medication usage or fasting glucose level above 126 mg/dL. Patients with total cholesterol 200 mg/dL or triglyceride 150 mg/dL were considered to have hyperlipidemia. Current smokers were defined as those who had smoked for some period during the past year. Family history of premature coronary heart disease in a first-degree relative heart attack, treated angina, percutaneous coronary catheter interventional procedure, or coronary artery bypass surgery, stroke or sudden cardiac death in a male parent or sibling before the age of 55 years or a female parent or sibling before the age of 65 years.

The results of the blood samples and analyses were obtained from the review of the patients' chart. All blood samples were drawn at the admission before coronary angiography. Hematological indices such as hemoglobin, white blood cell, platelet counts, and mean platelet volume were measured as part of the automated complete blood count using the simultaneous optical and impedance measurements (Cell Dyn 3700 Abbott Diagnostics, IL, USA). All routine biochemical tests were carried out on an automatic biochemical analyzer (Beckman Coulter AU640, Germany).

Selective coronary angiography was performed in multiple orthogonal projections using the Judkins technique. Angiograms were reviewed by two experienced angiographers who were blind to the clinical knowledge of patients. The CCC was graded using the Rentrop classification:[16] Grade 0 = no filling of any collateral vessel, Grade 1 = filling of side branches of the artery to be the epicardial segment, Grade 2 = partial filling of the epicardial artery by collateral vessels, and Grade 3 = complete filling of the epicardial artery by a collateral vessel. Patients were then divided into two groups according to their collateral grades. Group 1 (poor coronary collateral development) comprised patients with at least one vessel having ≥90% stenosis and grade-0 or grade-1 collaterals. Group 2 (well-coronary collateral development) consisted of patients with at least one vessel having ≥90% stenosis and Grade-2 or Grade-3 collaterals.

Statistical analyses were performed using the SPSS software version. 20 (SPSS Inc., Chicago, IL, USA). The variables were investigated using the visual (histograms and probability plots) and analytical methods (Shapiro Wilk's test) to determine whether they were normally distributed. Descriptive analyses are presented using the means and standard deviations for normally distributed variables. Mean, standard deviation, lowest median value, highest frequency value, and ratio value were used. The Kolmogorov–Simirnov test was used to assess the distribution of data. Analysis of variance followed by Tukey's *post hoc* method, the Kruskal–Wallis, and Mann–Whitney U-tests were used to analyze the quantitative data. The Chi-square test was used to analyze the qualitative data. Logistic regression analysis was used to determine the impact of variables. Standardized β coefficients and 95% confidence intervals (CI) were calculated. $P < 0.05$ was considered statistically significant.

Results

The demographic, clinical, laboratory, and angiographically data of the patients are summarized in Table 1. There were no statistically significant differences between the two groups, in terms of age, gender, and BMI and left ventricular systolic function ($P > 0.05$ for all). There were also no statistically significant differences between the groups in terms of cardiovascular risk factors, such as dyslipidemia, hypertension, diabetes mellitus, smoking, and family history ($P > 0.05$ for all). There was no statistically significant difference between the groups with respect to the medications of the patients ($P > 0.05$ for all).

Patient's angiographic characteristics (coronary collateral development level-Rentrop classification) are also summarized in Table 1. Among 221 patients with good CCC, 92 patients had Rentrop Grades 3 and 129 patients had Rentrop Grades 2. Among 134 patients with poor CCC, 86 patients had Rentrop grades 1 and 86 patients had no coronary collaterals.

Patient's biochemical and hematological features are summarized in Table 2. Monocyte to high-density lipoprotein ratio (12.5 ± 4.5 vs. 16.4 ± 5.7, $P < 0.01$), monocyte level (0.47 ± 0.12 vs. 0.58 ± 0.13 g/dL, $P < 0.01$), and neutrophil-to-lymphocyte ratio (2.9 ± 2.1 vs. 3.7 ± 2.4, $P < 0.01$) significantly higher in the well CCC group than in the poor CCC group [Table 2]. Lymphocyte level (2.21 ± 0.7 vs. 1.92 ± 0.8, $P = 0.018$) was significantly lower in the well CCC goup than in the poor CCC group. As for the other laboratory parameters, there were no statistically significant differences between the three groups ($P > 0.05$ for all).

When the patients with CCC were divided into four grading of collateral filling as Rentrop-0, Rentrop-I, Rentrop-II, and Rentrop-III, these groups have shown different MHR levels. We demonstrated that MHR levels are significantly related with the Rentrop classification of CCC in Table 3. In *post hoc* analysis, there was statistically significant difference in MHR levels between the some groups one by one. In the Rentrop III group, the MHR value was significantly higher ($P < 0.01$) than the Rentrop-0, Rentrop-I, and Rentrop-II group. In the Rentrop II group, the MHR value was significantly higher ($P < 0.01$) than in the group with Rentrop-0 and Rentrop-I. As a result, relatively high levels of Rentrop-III MHR to Rentrop-II MHR, Rentrop-I and Rentrop-0 MHR identified as a root cause behind the differentiations (respectively, mean value ± standart deviation; 17.5 ± 5.5, 15.6 ± 5.8, 12.7 ± 4.3, and 12.0 ± 4.9; $P < 0.01$).

Multivariate logistic regression test was employed for determining the independent predictors of well CCC [Table 4].

Table 1: Demographic, clinical, and angiographic characteristics of the study population

	Group 1 poor coronary collateral (n=134)	Group 2 well coronary collateral (n=221)	P
Age (years)	62.3±12.0	63.5±11.8	0.475 (NS)
Gender			
Female, n (%)	39 (29.1)	54 (24.4)	0.332 (NS)
Male, n (%)	95 (70.9)	167 (75.6)	
BMI (kg/m^2)	26.2±4.0	27.3±6.2	0.138 (NS)
Diabetes mellitus	36 (26.9)	62 (28.1)	0.808 (NS)
Hypertension, n (%)	93 (69.4)	153 (69.2)	0.114 (NS)
Systolic blood pressure (mmhg)	139.4±15.2	142.4±15.4	0.089 (NS)
Diastolic blood pressure (mmhg)	87.5±11.2	77.3±10.9	0.860 (NS)
Smoker, n (%)	63 (47.0)	110 (49.8)	0.614 (NS)
Dyslipidemia, n (%)	71 (52.9)	137 (61.9)	0.125 (NS)
Family history of CAD, n (%)	44 (32.8)	70 (31.6)	0.542 (NS)
Left ventricular EF (%)	52.5±9.2	51.7±9.2	0.388 (NS)
Medication			
ACEI use, n (%)	112 (83.6)	195 (88.2)	0.214 (NS)
Beta-blocker use, n (%)	117 (87.3)	201 (91.0)	0.277 (NS)
CC blocker use, n (%)	112 (83.6)	179 (81.0)	0.579 (NS)
Nitrates use, n (%)	48 (35.8)	62 (28.0)	0.106 (NS)
Trimethazidine use, n (%)	83 (61.9)	118 (53.3)	0.098 (NS)
Statin use, n (%)	63 (47.0)	77 (34.8)	0.140 (NS)
Fibrate use, n (%)	46 (34.3)	67 (30.3)	0.553 (NS)
Acetylsalicylicacid, n (%)	127 (94.7)	202 (91.4)	0.854 (NS)
Rentrop Classification			
Rentrop - 0, n (%)	48 (35.8)	0 (0.0)	<0.001
Rentrop - I, n (%)	86 (64.2)	0 (0.0)	
Rentrop - II, n (%)	0 (0.0)	129 (58.4)	
Rentrop - III, n (%)	0 (0.0)	92 (41.6)	

CAD: Coronary artery disease, EF: Ejection fraction, ACEI: Angiotensin-converting enzyme inhibitor, CC: Calcium channel, NS: Nonsense, BMI: Body mass ındex

Table 2: Biochemical and hematological parameters findings of the study population

	Group 1 poor coronary collateral (n=134)	Group 2 well coronary collateral (n=221)	P
White blood cell (10^3/μL)	8.49±2.24	8.56±2.71	0.891 (NS)
Hemoglobin (10^3/μL)	13.7±2.0	14.7±1.4	0.985 (NS)
Platelet (10^3/μL)	235±63.9	230.3±61.9	0.305 (NS)
Neutrophil (10^3/μL)	6.03±2.23	6.19±2.24	0.162 (NS)
Lymphocyte (10^3/μL)	2.21±0.7	1.92±0.8	0.018
Monosite (10^3/μL)	0.47±0.12	0.58±0.13	<0.001
Eosinophil (10^3/μL)	0.18±0.53	0.18±0.38	0.860 (NS)
Basophil (10^3/μL)	0.01±0.0	0.01±0.0	0.843 (NS)
Neutrophil/lymphocyte ratio	2.9±2.1	3.7±2.4	0.036
Platelet/lymphocyte ratio	0.1±0.1	0.1±01	0.974 (NS)
AST (U/lt)	21.7±8.4	23.1±6.1	0.189 (NS)
ALT (U/lt)	22.4±8.2	25.3±10.8	0.166 (NS)
TSH (mIU/L)	1.4±0.9	1.7±1.6	0.215 (NS)
FBG (mg/dl)	111.9±41.9	109.6±42.6	0.819 (NS)
Hemoglobin A_1c (%)	6.1±0.9	6.9±1.1	0.756 (NS)
Urea (mg/dl)	30.0±10.3	33.8±17.7	0.489 (NS)
Creatinine (mg/dl)	1.1±0.5	1.1±0.6	0.476 (NS)
Total cholesterol (mg/dl)	196.1±49.5	196.9±65.7	0.764 (NS)
LDL (mg/dl)	120.0±38.2	121.5±47.3	0.983 (NS)
HDL (mg/dl)	40.4±10.7	38.5±12.5	0.391 (NS)
Triglyceride (mg/dl)	182.6±126.1	163.4±87.7	0.704 (NS)
MHR	12.5±4.5	16.4±5.7	<0.001
THR	5.0±4.3	4.0±1.9	0.403 (NS)

Mean value±SD. ALT: Alanine transaminase, AST: Aspartate transaminase, FBG: Fasting blood glucose, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, MHR: Monocyte high-density lipoprotein ratio, NS: Nonsense, THR: Triglyceride high-density lipoprotein ratio, TSH: Thyroid-stimulating hormone, SD: Standard deviation

Table 3: Relationships between coronary collateral circulation severity and monocyte high-density lipoprotein ratio

	Mean±SD, median value (IQR)				
	Rentrop 0	Rentrop I	Rentrop II	Rentrop III	P
MHR	12.0±4.9, 11.2 (6)	12.7±4.3, 12.8 (5.4)	15.6±5.8, 14.9 (8.1)	17.5±5.5, 17.2 (8.3)	<0.001[K]

[K]Kruskal-Wallis (Mann-Whitney U-test). SD: Standard deviation, MHR: Monocyte high-density lipoprotein ratio, IQR: İnterquartile range

Table 4: Univariate and multivariate analyses of well-developed coronary collateral circulation

	Univariate model			Multivariate model		
	OR	95% CI	P	OR	95% CI	P
NLR	0.992	0.94-1.04	0.738			
Monocyte	1.013	1.01-1.02	<0.001	1.015	1.01-1.02	<0.001
Lymphocyte	1.000	1.00-1.00	0.914			
MHR	1.170	1.11-1.23	<0.001	1.212	1.14-1.29	<0.001

MHR: Monocyte high-density lipoprotein cholesterol ratio, NLR: Neutrophil-lymphocyte ratio, CI: Confidence interval, OR: Odds ratio

The variables that were found to have significance in the univariate analysis (neutrophil/lymphocyte ratio, monocyte, lymphocyte, and monocyte/HDL-C ratio) were included in the multivariate model. Among those, monocyte count and monocyte/HDL-C ratio (respectively; odds ratio [OR]: 1.015; 95% CI (1.01–1.02); $P < 0.01$ and OR: 1.212; 95% CI (1.14–1.29); $P < 0.01$) were found to be the independent predictors of well CCC.

Discussion

The main finding of the present study was that low MHR was associated with a significant impairment in coronary collateralization in patients with SCAD. We also found that MHR was significantly related with the Rentrop score of CCC grading. In addition, low MHR was an independent predictor of poor CCC in the multivariate analyses. This study provides the first evidence that low MHR is an independent predictor of poor CCC in patients with CAD.

The presence of well-collateral circulation has beneficial effects on left ventricular function, infarct size, and aneurysm formation.[17] A recent meta-analysis showed that patients with well collateralization have 36% reduced mortality risk compared with patients with poor collateralization.[5] Therapeutic promotion of collateral growth is a valuable treatment strategy in patients who cannot be revascularized by percutaneous coronary intervention or coronary artery bypass grafting. It is important to define the predictors of CCC development by further studying CCC and its physiopathological mechanisms.

Atherosclerosis is a maladaptive, nonresolving chronic low-grade inflammatory disease occurring at the sites of blood flow disturbance in the arterial tree.[18,19] The subendothelial retention of atherogenic lipoproteins (such as LDL and oxidized-LDL) at these sites and flow-mediated inflammatory changes in endothelial cells are thought to trigger the atherogenic process.[20,21] Monocytes as a distinct type of leukocytes have a key role during this process. It has been known that monocyte activation plays an important role in chronic low-grade inflammation and atherosclerotic cardiovascular disease.[14] In the center of this atherosclerotic plaque, macrophages derived from the monocytes take an active role by phagocytizing oxidized-LDL and forming the hazardous foamy cells. It has been shown that monocyte count was an independent and significant predictor of plaque formation and progression in atherosclerosis.[22] Contrary to monocytes, HDL-C interferes LDL oxidation and has anti-inflammatory, antioxidant, antithrombotic, and beneficial vascular effects.[23,24] These activities are provided by both the quality and quantity of HDL-C.[25] For this reason, monocytes show a proinflammatory action, but HDL-C functions as a reversal factor during this process.

Increased circulating monocyte count in diabetic and nondiabetic CAD patients was related to well-coronary collateral growth.[8,26] Furthermore, a recent study show that low HDL-C frequency was more frequent in the poor CCC than the well CCC group.[9] According to these, monocytes exert a proinflammatory effect, but HDL-C functions as a reversal factor during this process. However, the role of both monocytes and HDL-C was less known during the development of CCC. Coronary angiogenesis and collateral growth are chronic adaptations to myocardial ischemia, which are aimed at restoring coronary blood flow and salvaging myocardium in an ischemic region. MHR may be a simple novel marker that predicts collateral development. To our knowledge, no biochemical, hematologic, or enzymatic marker to could predict or determine alone collateral development is present. Perhaps, the MHR may be a somewhat more comprehensive marker for the emergence and development of CCC. MHR is a newly introduced inflammatory marker. Its relation with cardiovascular diseases has been studied only in a few studies. Recently, Kanbay *et al*. described a novel inflammatory marker that combined the predictive values of the circulating monocyte count and serum HDL cholesterol into a single proportion.[14] They showed that MHR was associated cardiovascular prognosis in patients with chronic kidney disease. Another recent study showed that higher MHR was associated with the burden of coronary atherosclerosis.[27] In the present study, which also included 243 patients, Altin *et al*. showed a significant positive correlation between the coronary calcium score, which is an indicator of CAD and MHR.[28]

On the basis of these findings and the pathophysiological role of inflammation in CCC, we hypothesized that the MHR may be associated with well CCC. In the present study, high MHR was found to be an independent predictor of the CCC development in patients with stable CAD.

This study has several limitations. First, this study is subject to the limitations inherent to a retrospective study, and the sample size in our study is relatively small. Second, a single measurement of MHR may not reflect lifetime status and coronary collateralization progresses over many years. Third, an important clinical data, the duration of symptoms was missing. In addition, study population is not homogenous. The study population may not reflect the whole population. Furthermore, angiographic details such as the involving vessels, lesions proximity, and severity of CAD were also missing. Furthermore, the classification of the Rentrop score was made without occluding the contralateral vessels, as it was suggested in the original manuscript about that subject. This visual method also has some other limitations: It is not a very objective method as it may be influenced by blood pressure, and the force of contrast injection as well as the duration of filming. We could not assess all potential factors that might involve the interaction between monocytes and HDL particles. Monocytes are not homogenous in behavioral response and have various types demonstrating different activities.[29] The classification of different monocyte subgroups may strengthen our results. The same situation also exists in HDL particles. Beyond the quantity of HDL particles, HDL particles can be classified based on size such as small, intermediate, and large HDL subtypes.[30] HDL particles and especially monocytes may be influenced by the several factors. The evaluation of atherogenic properties of these subtypes may have a contributed to our study.

Conclusion

This study showed that, in patients with stable CAD, MHR levels are significantly higher in patients with good CCC than in those with poor CCC. MHR may serve as an independent predictor of good CCC in patients with ≥90% coronary stenosis. However, further studies in different populations with larger sample size are needed to confirm these findings, and additional studies are necessary to address the underlying function and mechanism.

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Conflicts of interest

There are no conflicts of interest.

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