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The relationship between serum homocysteine levels and development of coronary collateral circulation in patients with acute coronary syndrome

Akut koroner sendromlu hastalarda serum homosistein düzeyleri ile koroner kollateral dolaşım gelişimi arasındaki ilişki

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ABSTRACT

Aim: Homocysteine is an amino acid that plays a role in folate metabolism and inhibits endothelial cell proliferation which is important for angiogenesis. In this study, we aimed to investigate the relationship between serum homocysteine levels and coronary collateral development.

Material and Method: Consecutive 176 patients, with acute coronary syndrome and chronic total occlusion, were divided into two groups according to coronary collateral development. Rentrop 0 and 1 were regarded as group I and Rentrop 2 and 3 as group II.

Results: Plasma homocysteine levels were 18.2±7.0 µmol/L in the group I and 15.7±5.1 µmol/L in the group II. Univariate logistic regression analysis showed that mean platelet volume and homocysteine were associated with poor coronary collateral. Multivariate logistic regression analysis showed that homocysteine level was independently associated with poor coronary collateral circulation (OR 1.069 [95% CI 1.012-1.130]; p=0.018).

Conclusion: In this study clearly demonstrates that high serum homocysteine level is associated with poor collateral development in patients with acute coronary syndrome.

Keywords: Coronary artery disease, coronary collateral circulation, homocysteine

ÖZ

Amaç: Homosistein, folat metabolizmasında rol oynayan, anjiyogenez için önemli olan endotelyal hücre proliferasyonunu inhibe eden bir aminoasittir. Bu çalışmada serum homosistein düzeyiyle koroner kollateral gelişimi arasındaki ilişkiyi araştırmayı amaçladık.

Gereç ve Yöntem: Kronik total oklüzyonu olan 176 hasta koroner kollateral gelişimine göre 2 gruba ayrıldı. Rentrop 0 and 1 olanlar grup I Rentrop 2 ve 3 olanlar grup II olarak kabul edildi.

Sonuç: Plazma homosistein düzeyleri grup I'de 18,2±7,0 µmol / L ve grup II'de 15,7±5,1 µmol / L olarak saptandı. Tek değişkenli lojistik regresyon analizi ortalama trombosit hacmi ve homosisteinin zayıf koroner kollateral ile ilişkili olduğunu gösterdi. Çok değişkenli lojistik regresyon analizi homosistein düzeyinin bağımsız olarak zayıf koroner kollateral dolaşım ile ilişkili olduğunu göstermiştir (OR 1,069 [%95 CI 1,012-1,130]; p=0,018).

Sonuç: Bu çalışmada yüksek serum homosistein düzeyinin akut koroner sendromlu hastalarda zayıf kollateral gelişim ile ilişkili olduğu açıkça görülmektedir.

Anahtar Kelimeler: Koroner arter hastalığı, koroner kollateral dolaşım, homosistein

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INTRODUCTION

Coronary collateral circulation (CCC) is a potential vessel that develops between different coronary arteries or sections of the same coronary artery to provide blood flow to the ischemic area in order to maintain the viability of the myocardium when a severe stenosis or total occlusion occurs that reduces blood flow in the coronary artery (1). Development of CCC plays a significant role in decreasing cardiovascular events and angina symptoms and preserving the myocardium from the ischemia (2-4). Coronary collateral vessels provide feeding of the ischemic myocardium by increasing blood supply when stenosis or complete occlusion of the coronary artery occurs. They play a crucial role in maintaining systolic function of the left ventricle in case of complete obstruction. Also previous studies have shown that collateral arteries also occur in patients without coronary artery disease (5). CCC does not develop in more than half of patients with coronary artery disease. Although the exact cause is unknown, genetic factors are thought to be responsible (6).

Homocysteine is an amino acid comprises of sulfide that plays a major role in folate metabolism and is produced by the demethylation of methionine (7). Homocysteine inhibits endothelial cell proliferation, which is important for angiogenesis. Nagai et al. (8) reported that hyperhomocysteinemia inhibited endothelial proliferation in vitro and angiogenesis in vivo. Therefore, we investigated that the relationship between homocysteine levels and the development of coronary collateral circulation in patients with acute coronary syndrome.

MATERIAL AND METHOD

The study population consisted of 176 consecutive patients with acute coronary syndrome and chronic total occlusion (CTO) in at least one major coronary artery detected during coronary angiography between June 2019 and December 2013. Coronary collateral status were graded from 0 to 3 according to the Rentrop's classification. Grade 0 = no visible filling of any collateral, grade 1= filling of the side branches of the artery, grade 2= partial filling of the epicardial vessel by way of collateral, grade 3= complete collateral filling of the epicardial vessel (9). Patients were divided into two groups according to coronary collateral development. Rentrop 0 and 1 were regarded as group I (poor collateral) and Rentrop 2 and 3 as group II (good collateral). In cases of discrepancy between the 2 reviewers on the collateral status, a third cardiologist was called in for a decision.

The exclusion criteria were the presence of any of the followings: acute/chronic renal failure, chronic obstructive lung disease, any malignancy, evidence of ongoing infection or inflammation, liver failure, previous history of heart failure, previous history of revascularization (percutaneous or surgical), moderate or severe valvular heart disease, peripheral arterial disease, hematological disorders, aortic dissection, pulmonary embolism, any thyroid and rheumatological disease.

Hemoglobin, white blood cell count, platelets, glucose, glycated hemoglobin (HbA1C), creatinine, cholesterol levels, and homocysteine were assessed. The homocysteine level was determined using a commercially available kit (Chromsystems Instruments & Chemicals GmbH Am Haag 12, 82166 Gräfelfing, Germany) by high-pressure liquid chromatography and fluorometric methods in blood samples with ethylenediaminetetraacetic acid.

Judkins technique was used for coronary angiography using a digital angiographic system (Siemens Axiom Artis zee 2011; Siemens Healthcare, Erlangen, Germany). All coronary arteries were visualized in at least two different projections. At least 50% stenosis was accepted as significant CAD. In cases of disagreement between the two calculations, a senior interventional cardiologist was consulted and a common consensus was obtained from the three operators.

Hypertension; defined as systolic blood pressure ≥140 mmHg and / or diastolic blood pressure ≥90 mmHg or use of antihypertensive drugs in at least two measurements. Diabetes mellitus; defined as fasting blood sugar ≥126 mg / dL or use of antidiabetic treatment. Hyperlipidemia; defined as fasting total cholesterol level ≥200 mg / dL or triglyceride level ≥150 mg / dL or use of lipid-lowering drugs. Smoking has been accepted as a smoker in the last 6 months.

Angiographic images were examined from coronary angiography unit records. Coronary angiographic records were examined by interventional cardiologists and stent restenosis; defined as a stenosis of more than 50% in the previously deployed stent or 5mm proximal or distal.

Transthoracic echocardiography (TTE) was performed for all patients within 48 hours after hospitalization (Vivid 9; GE Medical System, Horten, Norway). Left ventricular ejection fraction (LVEF) was measured using the Simpson method.

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0 for Windows (SPSS Inc., Chicago, IL). The chi-square test was used for comparison of categorical variables. Quantitative variables are expressed as the mean value ± SD for parametric variables, and median and quartiles for non-parametric variables. Continuous variables were analyzed for normal distribution using the Kolmogorov-Smirnov test and analyzed for homogeneity using the Levene tests. Comparisons of parametric values among groups were performed by the Student t-test and Mann-Whitney U test for non-parametric values. Categorical variables were compared with the chi-square test. Multiple logistic regression analysis was used to determine the effects of parameters on the development of collaterals. A two-tailed $p<0.05$ was considered significant.

Ethical Declaration

The study was carried out subsequent to receiving permission for its conduct from the presiding local Ethics Committee (Permission Granted 21.08.2019, Decision No. 2019.08.10).

RESULTS

A total of 176 patients, 120 in group I and 56 in group II,

were included in the study. The mean age of the patients were 62.7±13.2 years in first group and 66.7 ± 11.1 years in second group. There was no difference between the 2 groups in terms of body mass index, sex, hypertension, diabetes mellitus, smoking, dyslipidemia, blood pressure, and left ventricular ejection fraction. The mean age of the patients was higher in group II than group I (p= 0.04) (**Table 1**).

Table 1. Main clinical and angiographic features of the study population

	Group I (n=120)	Group II (n=56)	p
Age (years, mean ± SD)	62,7 ± 13,2	66,7 ± 11,1	**0,04**
Body mass index	26,1 ± 4,4	30,5 ± 2,5	0,16
Male sex	76 (63,3%)	37 (67,3%)	0,61
Hypertension	65 (55,1%)	27 (49,1%)	0,46
Diabetes mellitus	45 (38,1%)	18 (32,7%)	0,49
Smoking	50 (42,4%)	19 (34,5%)	0,32
Dyslipidemia	32 (27,1%)	22 (40,0%)	0,08
Systolic blood pressure, mm Hg	132 ± 26	125 ± 21	0,11
Diastolic blood pressure, mmHg	77 ± 15	76 ± 13	0,48
Ejection fraction (%)	48 ± 10	46 ± 9	0,36

SD: Standart deviation

The hematological and biochemical parameters of the groups are listed in Table 2. White blood cell (WBC) count, hemoglobin, platelets were similar in both groups. Mean platelet volume (MPV) was higher in the group I. There was no difference between the groups in terms of biochemical parameters except homocysteine. Plasma homocysteine levels were 18.2 ± 7.0 µmol/L in the group I and 15.7 ± 5.1 µmol/L in the group II. Homocysteine levels were higher in the group I compared to the group II (p= 0.02).

Tablo 2. Comparision of baseline blood features in the groups

	Group I (n=120)	Group II (n=56)	p
White blood cells (×10³ µL)	9.9±3.2	10.0±3.1	0.91
Hemoglobin (gr/dl)	13.7±1.9	13.4±1.9	0.28
Mean platelet volume (fL)	9.0±1.1	8.6±1.0	**0.03**
Platelets (×10³ µL)	245±81	225±80	0.13
Glucose (mg/dl)	153 (98-184)	142 (97-158)	0.57
Creatinine (mg/dl)	1.1±0.3	1.1±0.3	0.21
Üric acid (mg/dl)	5.6±1.4	5.8±1.6	0.34
Albumin (g/dl)	3.8±0.4	3.7±0.5	0.29
Total cholesterol (mg/dl)	194±60	179±60	0.14
LDL-C (mg/dl)	122±44	109±43	0.07
HDL-C (mg/dl)	40±11	39±9	0.62
Triglyceride (mg/dl)	176 (98-189)	138 (83-181)	0.16
Homocysteine (µmol/L)	18.2±7.0	15.7±.1	**0.02**
Fibrinogen (mg/dl)	427±134	419±106	0.67
Hs-CRP (mg/L)	6.9 (2.9-0.6)	7.4 (2.9-0.9)	0.24

LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol, Hs-CRP: High sensitive C-reactive protein

Univariate logistic regression analysis showed that MPV and homocysteine were associated with poor coronary collateral (**Table 3**). Multivariate logistic regression analysis showed that homocysteine level was independently associated with poor coronary collateral circulation (OR 1.069 [95% CI 1.012-1.130]; P= 0.018) (**Table 3**).

Table 3. Logistic regression analysis

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.026 (0.999-1.052)	0.055		
Dyslipidemia	1.792 (0.912-3.519)	0.090		
Glucose	0.998 (0.994-1.003)	0.424		
LDL-C	0.994 (0.986-1.001)	0.103		
MPV	1.374 (1.028-1.838)	**0.032**	1.335 (0.993-1.795)	0.056
Hs-CRP	1.031 (0.947-1.122)	0.482		
Homocysteine	1.074 (1.017-1.134)	**0.010**	1.069 (1.012-1.130)	**0.018**

MPV: mean platelet volume, LDL: low density lipoprotein cholesterol, Hs-CRP: high sensitive C-reactive protein, OR: odds ratio, CI: confidence interval

DISCUSSION

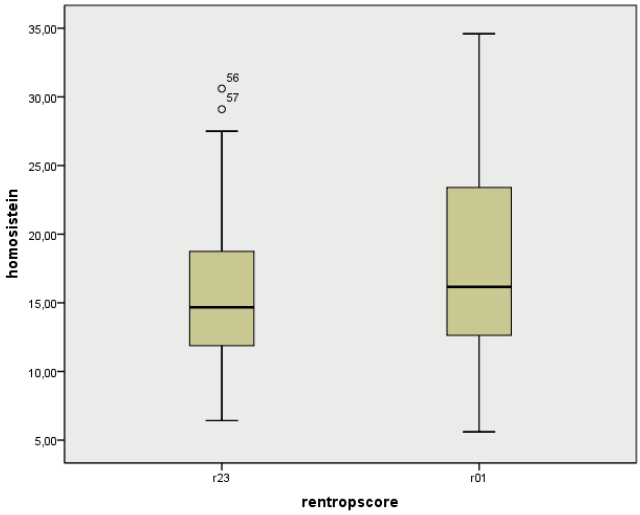

Figure 1. Comparison of serum homocysteine levels among Rentrop collateral grades

In the present study, we investigated the relationship between serum homocysteine levels and coronary collateral development in patients with chronic total occlusion. Our findings showed that serum homocysteine levels were higher in the poor collateral group than the good collateral group in patients with acute coronary syndrome and CTO. In addition, higher homocysteine levels were found as an independent predictor of poor collateral circulation.

Coronary collateral circulation plays an important role in maintaining systolic function of the left ventricle when stenosis or complete occlusion of the coronary artery occurs (10). The development of good collateral circulation may reduce the infarct area after total occlusion of the coronary artery and prevent systolic function of the left ventricle. Many clinical studies have shown that chronic hypoxia

trigger the activation of angiogenesis and arteriogenesis (8,11). The most important triggers for angiogenesis is shear stress at the endothelium. When the development of obstruction of a major artery, a steep pressure gradient develops across the collateral anastomoses and this pressure gradient is the driving force for an enhancement in blood flow through the collateral arterioles, leading to an augmented fluid shear stress that increases the collateral arteriolar endothelium (11). Some of the factors involved in the development of CCC have been studied in many studies. Several hematological and biochemical factors have been revealed to be associated with the degree of the collateral development.

Sayar et al. (12) found no correlation between plasma homocysteine concentration and coronary collateral development. But Nagai et al. (13) revealed that hyperhomocysteinemia negatively affected the development of coronary collaterals. And Yang et al. (14) found that serum level of homocysteine is independently and negatively associated with the development of collateral circulation in severe coronary artery stenosis. In this study, hyperhomocysteinemia was found to negatively affect the collateral development in accordance with the other two studies. Previous studies have shown that homocysteine stimulates vascular smooth muscle proliferation and decreases nitric oxide levels through inhibiting nitric oxide synthetase enzyme (15-17). As homocysteine inhibits endothelial cell proliferation, which plays an important role in angiogenesis, its elevation is expected to inhibit collateral development.

In the current study, we found that good collateral circulation with increasing age. Sahin et al. (18) have found that the age in the good collateral was higher than in the poor collateral. Shen et al. (19) reported that age was significantly higher in poor collateralization group.

The larger platelets, produced from megakaryocytes in the bone marrow, have greater prothrombotic potential than smaller (20). Previous studies have reported that MPV levels were significantly higher in the poor CC group compared with the good CC group (21,22). In our study, MPV was found to be higher in poor CC group, similar to other studies. Because of prothrombotic agents released from larger platelets may increase endothelial dysfunction more.

There are some limitations of our study. The major limitation is that the angiographically visualized collaterals are only part of the total collateral circulation. Because collateral vessels less than 100μm in diameter cannot be evaluated. The second this a single-centered study. The third the study was the small sample size so further studies with larger number of patients were needed.

CONCLUSION

In this study, we found that high serum homocysteine level is associated with poor collateral development in patients with acute coronary syndrome. Homocysteine treatment is not routinely applied for patients who have high homocysteine levels so we suggest that it is important to treat hyperhomocysteinemia in CAD patients, especially in those with poorly developed collaterals.

DECLARATION OF CONFLICTING INTERESTS

The author declared no conflicts of interest with respect to the authorship and/or publication of this article.

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