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The Association between Serum Endoglin Level and Coronary Collateral Vessel in Patients with Acute Coronary Syndromes

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ABSTRACT

Background: Previously, endoglin, also known as CD105, was shown to be related to angiogenesis.

Objectives: The present study aimed to investigate the relationship between endoglin levels and development of Coronary Collateral Circulation (CCC) in patients with acute coronary syndrome.

Patients and Methods: The study patients who underwent coronary angiography were divided into a poor collateral group (Group 1, N = 45) and a good collateral group (Group 2, N = 42), according to Rentrop classification. After recording the baseline characteristics, including age, Body Mass Index (BMI), systolic and diastolic blood pressures, smoking, history of hypertension, diabetes mellitus, and family history of Coronary Artery Disease (CAD), blood samples were taken for analysis of endoglin and other biochemical variables. The data were statistically analyzed using Mann-Whitney U test, independent sample t-test, chi-square test, ANOVA, Pearson's or Spearman's correlation tests, Receiver–Operating Characteristics (ROC) curve analysis, and multivariate logistic regression analysis. P values < 0.05 were considered as statistically significant.

Results: Endoglin levels were significantly higher in Group 1 compared to Group 2 (13.6 ± 3.8 vs. 10.2 ± 2.9 ng/mL, P < 0.001). Serum endoglin levels were negatively correlated to age, C-Reactive Protein (CRP), and Low Density Lipoprotein-Cholesterol (LDL-C) levels. Moreover, ROC analysis (area under curve: 0.758; 95% CI: 0.655-0.844; P < 0.001) provided a cutoff value of ≤ 12.6 ng/mL for endoglin to predict good CCC with 85.7% sensitivity and 60% specificity. In multivariate logistic regression analysis, endoglin levels (OR = 0.97; 95% CI: 0.95 – 0.99; P = 0.002) and presence of total occlusion (OR = 2.51; 95% CI: 1.05 – 5.8; P = 0.036) were predictors of good CCC.

Conclusions: Lower plasma endoglin levels were associated with better CCC development.

►*Implication for health policy/practice/research/medical education:*
Up to now, no studies have investigated the relationship between endoglin levels and coronary collateral vessels in patients with acute coronary syndromes. Increased endoglin levels are related to poor coronary collateral circulation in acute coronary syndromes. Endoglin levels might be promising in identifying patients with AMI and good coronary collateral circulation during hospitalization.

1. Background

A well-developed coronary collateral artery serves an alternative source of blood supply to the myocardium during ischemic episodes. These vessels develop as a protective response to ischemia, especially during Unstable Angina Pectoris (USAP) or Acute Myocardial Infarction (AMI). Good collateral flow protects from tissue damage and infarction and preserves contractile function (1, 2).

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Substantial predictors of collateral development include the severity of coronary stenosis (3), presence of Diabetes Mellitus (DM) (4), levels of inflammatory cells, and some growth factors (5-8).

Recently, endoglin was shown to be closely related to angiogenesis. Endoglin, also known as CD105, is a homodimeric membrane glycoprotein that regulates several Transforming Growth Factor (TGF) signaling pathways. Endoglin is also a component of the TGF-β receptor complex, predominantly expressed in endothelial cells, and enters the systemic circulation in soluble form. Increased endoglin levels have been shown to inhibit TGF-β signaling in the vessel wall (9). Piao et al. (10) reported an increased expression of endoglin in atherosclerotic coronary arteries. Endoglin plays a role in cardiovascular diseases, such as coronary artery disease (11), preeclampsia (12), Hypertension (HT), and DM. Endoglin also contributes to the process of plaque neovascularization (13, 14).

Development of Coronary Collateral Circulation (CCC) may differ among patients with a similar degree of coronary artery stenosis, even total coronary occlusion (15). Inducing angionesis is clinically important for preventing future cardiac events in patient with Coronary Artery Disease (CAD), and the serum levels of molecules involved in angiogenesis facilitate neovascularization in such patients.

2. Objectives

This study aims to investigate the relationship between endoglin level and CCC development in patients with acute coronary syndrome.

3. Patients and Methods

3.1. Study Design and Population

This prospective study was conducted on 87 patients (aged 36 – 87 years) with acute coronary syndrome who underwent coronary angiography. After a routine cardiologic examination, one cardiologist performed electrocardiographic and echocardiographic (Esaote MyLab 50, Genoa, Italy) evaluations on all the patients to identify acute coronary syndrome and to exclude the patients with congestive heart failure and any moderate to severe valvular disease. Acute coronary syndrome was diagnosed according to the criteria recommended by the American College of Cardiology/American Heart Association (16). The patients were divided into two groups based on poor and good coronary collateral vessels. Group 1 consisted of 45 patients with poor CCC and Group 2 consisted of 42 patients with good CCC.

Baseline characteristics, including history of HT, DM, smoking, and family history of CAD, were recorded. HT was defined as Blood Pressure (BP) > 140/90 mmHg according to two different sphygmomanometer measurements or having a history of antihypertensive drugs use (17). Besides, DM was defined by the American Diabetes Association criteria (18). Dyslipidemia was also defined as serum Total Cholesterol (TC) ≥ 220 mg/dL, serum Triglyceride (TG) ≥ 200 mg/dL, Low-Density Lipoprotein-Cholesterol (LDL-C) ≥ 130 mg/dL, High-Density Lipoprotein-Cholesterol (HDL-C) < 35 mg/dL, or use of any lipid-lowering medications. Current smokers were defined as having a history of smoking within the past year. Body Mass Index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Patients with previous myocardial infarction, previous revascularization history, heart failure (Left Ventricle Ejection Fraction (LVEF) < 40%), chronic obstructive pulmonary disease, anemia, chronic liver disease, any systemic disease, kidney failure (serum creatinine >1.5 mg/dL), heart valve disease, thyroid disorders, intermittent cladication, and previous diagnosis of malignancy as well as anti-inflammatory drug users were excluded from the study. It should be noted that no diabetic patients from either group currently took insulin. Age, BMI, systolic and diastolic BPs, smoking, DM, and hyperlipidemia were recorded for both groups. All the study patients had neither any systemic disease nor a history of cerebrovascular accidents. A local Ethics Committee approved the study and all the participants gave their informed consents. The study protocol also conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

3.2. Laboratory Analysis

Antecubital venous blood samples were collected from all the patients on admission to the Coronary Care Unit and 48 hrs later for measurement of fasting glucose, TC, TG, HDL-C, LDL-C, C-Reactive Protein (CRP), troponin T, Creatine Kinase MB (CK-MB), and endoglin. A complete blood cell count was also determined using a Roche Sysmex XT-2000i autoanalyser (Roche Diagnostics, Paris, France) and the same commercial kits. Fasting glucose, TC, HDL-C, LDL-C, and TG levels were measured using a standard enzymatic method (AU680 auto-analyzer, Beckman Coulter, Brea, CA). In addition, CRP level was measured using a standard nephelometry method (Cobas311, Roche Diagnostics, Mannheim, Germany) with a sensitivity of 0.1 mg/L. For endoglin measurement, plasma was separated and stored at –80°C. Then, the blood samples were centrifuged at 15000 g for 15 minutes. After that, serum endoglin level was measured by standard quantitative sandwich ELISA (Quantikine) kits (R&D System, Minneapolis, MN, USA) according to the manufacturer's instructions. The assay's sensitivity was 0.007 ng/mL, intra-assay Coefficient of Variation (CV) was < 3.2%, and inter-assay CV was <6.7%.

3.3. Coronary Angiography

Two experienced cardiologists blinded to the study performed coronary angiography in the first three hours following the first admission using the standard Jutkins technique (Integris, Philips Medical Systems, Eindhoven, Netherlands). Angiographic characteristics, including grade of CCC and percentage of stenosis of all coronary lesions, were determined via a comprehensive review of the angiograms. Severe coronary artery stenosis was considered to be ≥ 90% luminal diameter stenosis in at least one major epicardial coronary artery. Additionally, CCC was graded using the Rentrop classification as follows (19): grade 0, no visible filling of any collateral vessels; grade 1, filling of side branches of the artery to 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. Grades 0 and 1 were

included in Group 1, while grades 2 and 3 were included in Group 2. Both groups 1 and 2 consisted of patients with at least one vessel having ≥ 90% stenosis. If the patients had more than one collateral vessel with a luminal stenosis of 90% or greater, the collateral vessel with the highest Rentrop grade was accepted for collateral grading.

3.4. Statistical Analysis

The study data were analyzed using the Predictive Analysis Software Statistics 18 (SPSS Inc., Chicago, Illinois). Variable distributions were checked using Shapiro-Wilk normality test. Then, non-normally and normally distributed variables in the two groups were compared using Mann-Whitney U test and independent sample t-test, respectively. In addition, categorical data, such as gender, HT, smoking, diabetes, and dyslipidemia, were compared using chi-square test and were expressed as numbers and percentages. ANOVA was also used to compare endoglin levels according to Rentrop classification. P values < 0.05 were considered as statistically significant. Pearson's or Spearman's correlation test was used to evaluate the correlation between endoglin and other variables. Moreover, Receiver–Operating Characteristics (ROC) curve analysis was performed using Medical Calculator software (Version 12.5.0, Ostend, Belgium) to establish the best cutoff value of endoglin for predicting the presence of good CCC. After determining the univariate predictors with P < 0.01, multivariate logistic regression analysis was performed to detect the independent variables for the presence of good CCC.

4. Results

The demographic and clinical characteristics of the patients have been presented in Table 1. Accordingly, mean age of the patients in Group 1 and Group 2 was 61 ± 11 and 62.5 ± 12 years, respectively (P = 0.554). Additionally, 57.7% of the patients in Group 1 and 69% of those in Group

Table 1. Clinical and Demographic Characteristics of the Study Groups

	Group 1 Poor N = 45	Group 2 Good N = 42	P value
Age, years	61 ± 11	62.5 ± 12	0.554 [a]
Male, n (%)	26(57.7)	29(69)	0.276 [c]
Body mass index, kg/m²	30.2(24 - 40)	30.5(23 - 42)	0.155 [b]
Current smoker, n (%)	29(64.4)	26(61.9)	0.806 [c]
Family history of CAD, n(%)	24(53.3)	18(42.8)	0.328 [c]
Dyslipidemia, n (%)	17(37.7)	19(45.2)	0.480 [c]
Diabetes, n (%)	13(28.9)	10(23.8)	0.591 [c]
Hypertension, n (%)	30 (66.6)	34 (80.9)	0.131 [c]
Patients with AMI, n (%)	38(84.4)	26(61.9)	0.001 [c]
Patients with USAP, n (%)	7(15.5)	16(38.1)	0.001 [c]
Duration of AP, minutes	121 ± 36	130 ± 31	0.234 [a]
RAS blocker, n (%)	23(51.1)	22(52.3)	0.906 [c]
Diuretic, n (%)	6(13.3)	7(16.7)	0.663 [c]
CCB, n (%)	10(22.2)	11(26.2)	0.666 [c]
Beta blocker, n (%)	7(15.5)	8(19)	0.667 [c]
Statin, n (%)	6(13.3)	9(21.4)	0.318 [c]
Aspirin, n (%)	10(22.2)	13(30.9)	0.356 [c]
Clopidogrel, n (%)	8(17.7)	6(14.2)	0.658 [c]
OAD, n (%)	11(24.4)	9(21.4)	0.738 [c]
Systolic BP, mmHg	132 ± 17.5	133 ± 17	0.956 [a]
Diastolic BP, mmHg	69(60 - 80)	71(60 - 80)	0.429
Glucose, mg/dL	118(72 - 265)	119(45 - 319)	0.694
Total cholesterol, mg/dL	193 ± 46	209 ± 37	0.075 [a]
Triglycerides, mg/dL	154(34 - 389)	189(77 - 576)	0.061 [b]
HDL cholesterol, mg/dL	43(23 - 75)	43.5(15 - 82)	0.586 [b]
LDL cholesterol, mg/dL	118 ± 38	128 ± 32	0.205 [a]
Creatinine, mg/dL	0.83 ± 0.40	0.93 ± 0.36	0.346 [a]
C-reactive protein, mg/dL	12(2 - 38)	16(3 - 45)	0.017 [b]
Endoglin, ng/mL	13.6 ± 3.8	10.2 ± 2.9	< 0.001 [a]
Troponin T, pg/mL	18(0.30 - 50)	13(0.06 - 80)	0.121 [b]
Creatine kinase MB, mg/dL	59(5 - 195)	45(2 - 114)	0.192 [b]
Left ventricle ejection fraction (%)	55(41 - 69)	52(35 - 65)	0.120 [b]
Presence of total occlusion, n(%)	14(31.1)	28(66.6)	0.001 [c]
Vessel with severe stenosis			
RCA, n(%)	22(48.8)	34(80.9)	0.002 [c]
CX, n(%)	19 (42.2)	25(59.5)	0.107 [c]
LAD, n(%)	33(73.3)	36(85.7)	0.154 [c]

Abbreviations: AMI, acute myocardial infarction; AP, angina pectoris, BP, blood pressure; CAD, coronary artery disease; CCB, calcium channel blocker; CX, Circumflex; HDL, high- density lipoprotein; LDL, low-density lipoprotein; LAD, left anterior descending artery, MB; myocardial band, RCA, right coronary artery; OAD, oral antidiabetic drug; USAP, unstable angina pectoris.
[a] Student t test, [b] Mann-Whitney U test,[c] Chi-square test

2 were male (P = 0.276). Group 1 and Group 2 patients shared similar demographic characteristics regarding BMI, HT rates, DM, dyslipidemia, smoking status, family history of CAD, and percentage of the patients treated with antihypertensive drugs or statins, oral antidiabetics, aspirin, or clopidogrel. However, the ratio of patients with AMI was higher in Group 1 (84.4% vs. 61.9%, P = 0.001), while the ratio of patients with USAP was higher in Group 2 (15.5% vs. 38.1%, P = 0.001).

Laboratory parameters of the study groups were similar in terms of systolic and diastolic BP, fasting glucose level, TC, TG, HDL-C, LDL-C, troponin T, and CK- MB, and LVEF (P > 0.05). However, endoglin levels were significantly higher in Group 1 than in Group 2 (13.6 ± 3.8 vs. 10.2 ± 2.9 ng/mL, P < 0.001) (Figure 1). On the other hand, the rates of presence of total occlusion and severe Right Coronary Artery (RCA) stenosis were higher in Group 2 compared to Group 1 (P = 0.001 and P = 0.002, respectively) (Table 1). Considering Rentrop groups, the highest and lowest endoglin levels were related to Rentrop groups 0 and 3, respectively (Rentrop 0: 14.7 ± 3.5, Rentrop1: 10.8 ± 3.3, Rentrop 2: 10.8 ± 3.2, and Rentrop 3: 9.6 ± 2.4 ng/mL; P < 0.001) (Figure 1).

Serum endoglin levels were negatively correlated to age, CRP and LDL-C levels (Figure 2), but were not correlated to other variables, including systolic and diastolic BP, fasting glucose level, TC, TG, HDL-C, troponin T, CK-MB, and LVEF (P > 0.05) (Table 2).

The ROC curve analysis showed that 12.6 ng/mL endoglin level had 85.7% sensitivity and 60% specificity for prediction of presence of good CCC (area under the curve = 0.758; 95% CI: 0.655 - 0.844; P < 0.001) (Figure 3).

Serum endoglin levels, presence of total occlusion, presence of severe stenosis in RCA, presence of AMI, presence of USAP, TG, and TC were entered as univariate variables into regression analysis to determine the presence of good CCC. In multivariate analysis, endoglin level (OR = 0.97; 95% CI: 0.95 – 0.99; P = 0.002) and presence of total occlusion (OR = 2.51; 95% CI: 1.05 – 5.8; P = 0.036) were significant variables associated with the presence of good coronary collateral vessels (Table 3).

5. Discussion

The present study demonstrated that (1) plasma endoglin

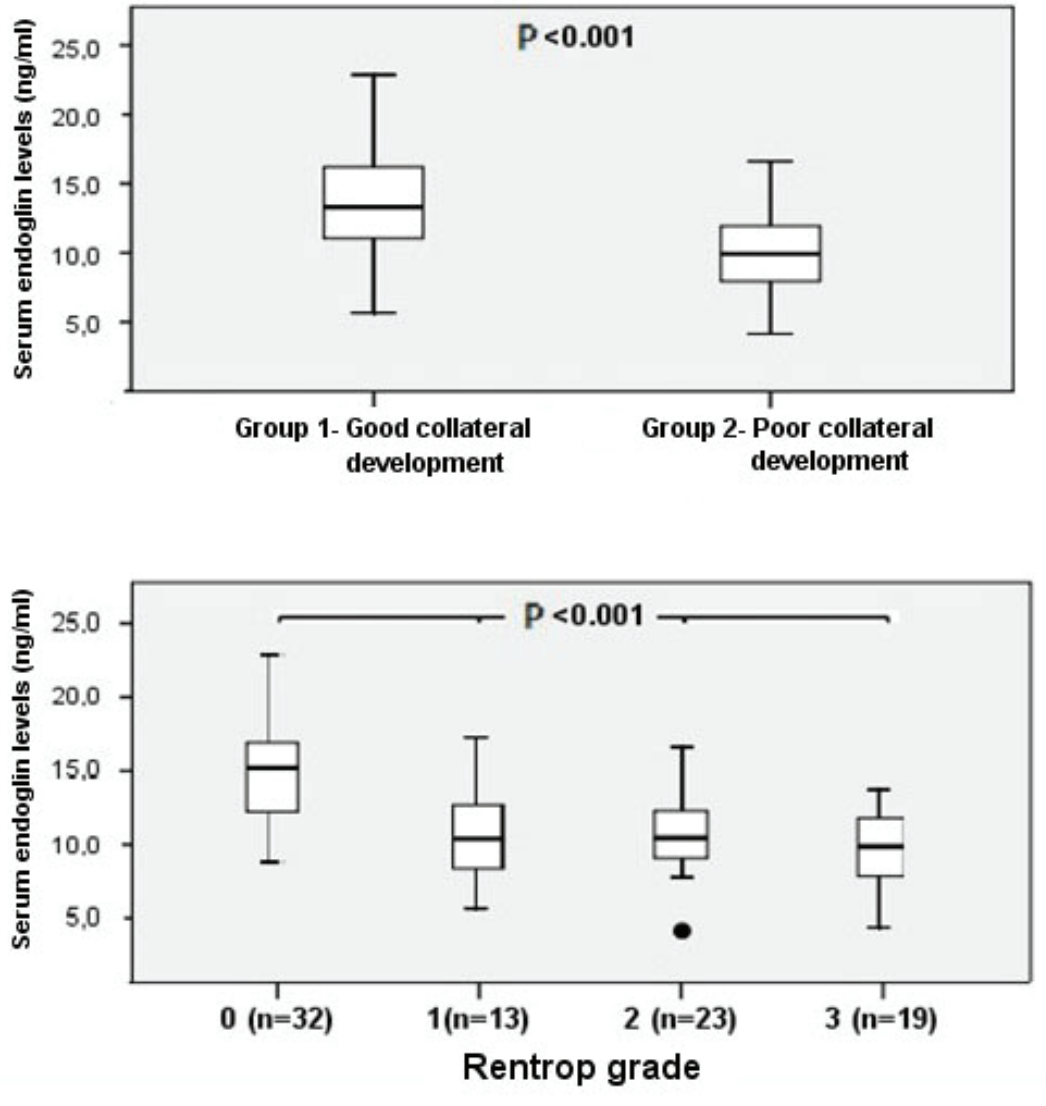


Figure 1. Comparisons of Endoglin Levels between Group 1 and Group 2 and Endoglin Levels According to Rentrop Groups

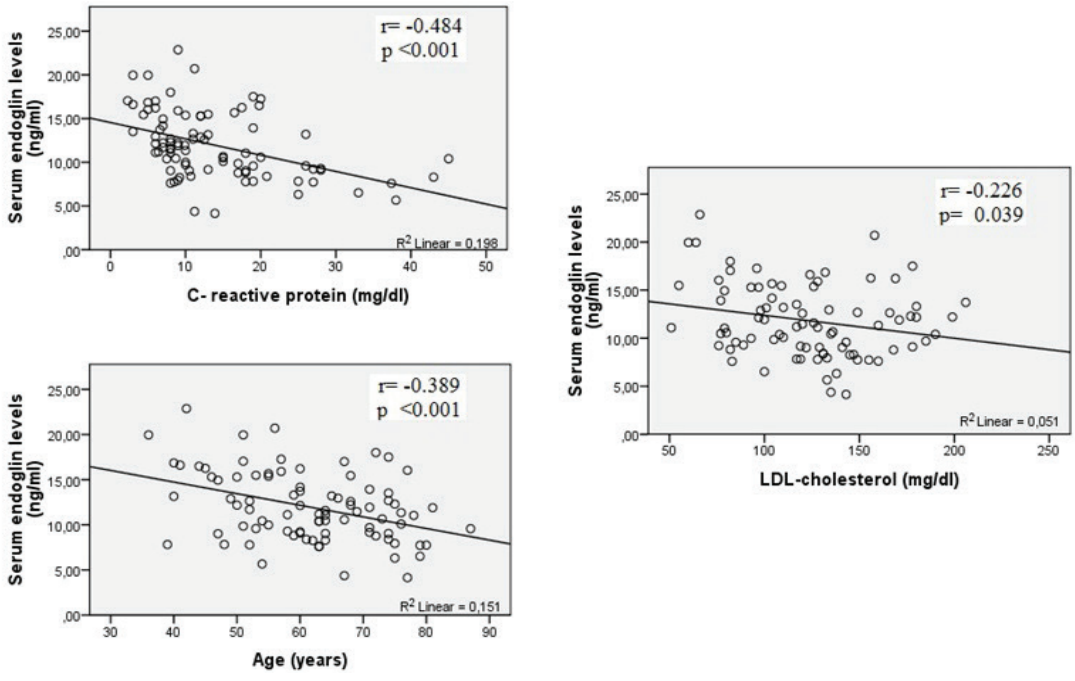


Figure 2. There Were Negative Correlations between Endoglin and CRP and Age and LDL-Cholesterol

Table 2. Correlations between Serum Endoglin Levels and Other Parametric Variables in Both Groups

	r	P
Age	-0.389	< 0.001 [a]
Body mass index	0.043	0.695 [b]
Systolic BP, mmHg	-0.072	0.510 [a]
Diastolic BP, mmHg	0.152	0.160 [b]
Glucose, mg/dL	0.109	0.319 [b]
Total cholesterol, mg/dL	-0.157	0.146 [a]
Triglycerides, mg/dL	-0.155	0.153 [b]
HDL cholesterol, mg/dL	-0.086	0.429 [b]
LDL cholesterol, mg/dL	-0.226	0.039 [a]
Creatinine, mg/dL	-0.03	0.978 [a]
C-reactive protein, mg/dL	-0.484	< 0.001 [b]
Troponin T, pg/mL	-0.140	0.197 [b]
Creatine kinase MB, mg/dL	-0.172	0.111 [b]
Left ventricle ejection fraction(%)	-0.054	0.617 [b]

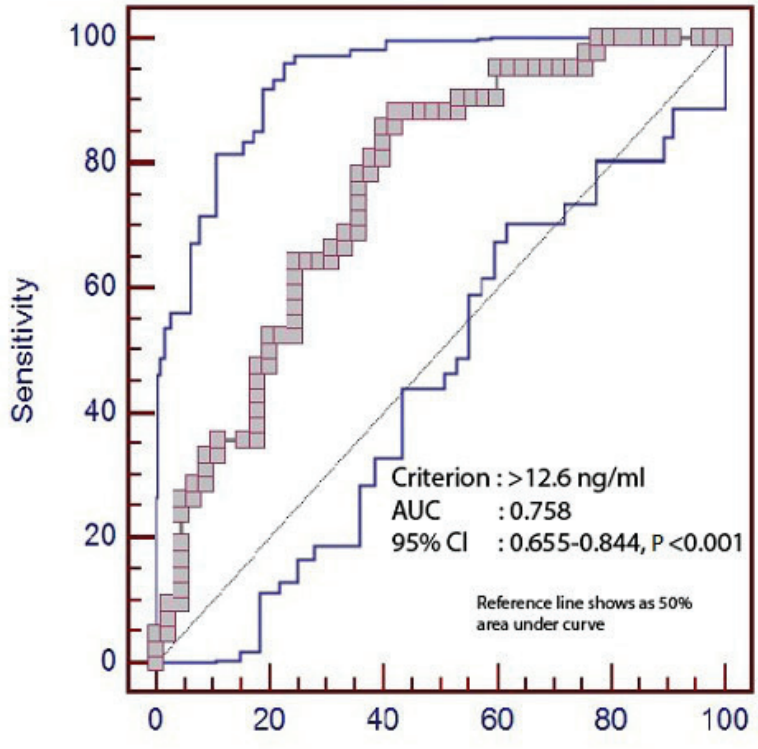
Abbreviations: BP, blood pressure; MB, myocardial band isoenzyme
[a] Pearson's correlation test, [b] Spearman's correlation test

level < 12.6 ng/mL and presence of total occlusion were significant independent factors predictive of good coronary collateral development in patients with acute coronary syndrome, and (2) plasma endoglin levels were negatively correlated to age, CRP, and LDL-C. We speculate that increased serum endoglin levels higher than 12.6 ng/mL indicate poor coronary collateral development and could be a novel marker that predicts the presence of coronary collateral vessels in patients with acute coronary syndrome.

To the best our knowledge, no existing clinical study has investigated the role of endoglin in development of coronary collateral vessels in patients with acute coronary syndrome. The present study is the first to show that increased endoglin level was an independent predictor of poor coronary artery collateral development. Although patients with poor coronary collateral vessels (Group 1) had lower TG and TC levels, the differences were not statistically significant. Lipid values may vary during AMI (20). The present study results revealed a negative correlation between LDL-C and endoglin. In accordance with our finding, Blaha et al. (21) found an association between hypercholesteremia and increased endoglin levels. Interestingly, statin treatment decreased serum endoglin levels in a rat atherosclerotic model (22). Furthermore, higher endoglin levels were found to be associated with higher vascular complication rates in patients with DM and more damaged target organs in HT (23). The ratios of patients with DM, smoking, HT, and dyslipidemia and the percentage of those treated with antihypertensive drugs or statins did not differ between the study groups; therefore, our findings were reliable.

Endoglin has an inhibitory effect on TGF-β mediated

Figure 3. ROC Curve Analysis of Endoglin for the Prediction of Good Collateral Development



AUC, Area under curve; sensitivity: 85.7% spesifity: 60%

Table 3. Univariate and Multivariate Regression Analyses of Independent Variables for Predicting Good Collateral Development

Variable	Univariate			Multivariate		
	R O	95% CI	P value	R O	95% CI	P value
Endoglin	0.97	0.95 - 0.98	< 0.001	0.97	0.95 - 0.99	0.002
Presence of total occlusion	4.41	1.8 - 10.8	0.001	2.51	1.05 - 5.8	0.036
Severe stenosis in RCA	4.56	1.7 - 11.6	0.001	1.95	1.08 - 6.5	0.452
Presence of AMI	0.39	0.14 - 0.58	0.001	0.45	0.15 - 2.1	0.311
Presence of USAP	3.42	2.1 - 12.7	0.001	2.21	0.47 - 10.3	0.450
Total cholesterol	1.01	0.99 - 1.01	0.078	1.01	0.99 - 1.02	0.245
Triglycerides	1.01	0.99 - 1.02	0.086	1.01	0.99 - 1.1	0.884
C-reactive protein	1.05	1.0 - 1.1	0.051	0.98	0.91 - 1.05	0.631

Abbreviations: AMI, acute myocardial infarction; RCA, right coronary artery, USAP; unstable angina pectoris

endothelial Nitric Oxide Synthase (eNOS) activation in endothelial cells (24), a key enzyme for Nitric Oxide (NO) production. Decreased NO triggers endothelial dysfunction and atherosclerosis. Endoglin also affects TGF-β signaling in Smooth Muscle Cells (SMCs). Hence, endoglin plays a role in regulation of vascular tone. Increased soluble endoglin levels induce hypertension (25). Although normal arteries show a weak endoglin expression, diseased arteries show a higher expression of endoglin by macrophages, SMCs, and endothelial cells (10). Endoglin levels increase in atherosclerosis vessels due to atherogenic stimuli, reflecting response to vessel wall injury.

Interestingly, endoglin may take part in formation of new blood microvessels (14). The relevance of endoglin to the cardiovascular system has been well demonstrated in Hereditary Hemorrhagic Telangiectasia (HHT), called Rendu Osler Weber syndrome (26). Expression of endoglin decreases in HHT, which is characterized by vascular dysplasia, arteriovenous malformation, and frequent episodes of epistaxis (27). In other words, lower endoglin levels are associated with increased arteriovenous malfarmations. Abnormal endothelial cells proliferate in the absence of endoglin due to a mutated endoglin gene, as such endoglin is required to maintain normal capillary beds and the diameter of small vessels (28). However, microvessels can facilitate transport of inflammatory cells to atherosclerotic plaques (29), and certain cytokines such as Vascular Growth Factor (VGF) and TGF-β secreted by these cells trigger a new angiogenic process inside the plaques (30). Luque et al. (14) showed increased endoglin expression in intimal neovessels in carotid artery plaques. While the plaques with few areas of inflammation were generally stable and uncomplicated (31), unstable plaques were associated with increased neoangiogenic activity and increased inflammatory infiltration and were generally prone to hemorrhage and rupture (14, 32). Hence, increased

soluble endoglin levels may be associated with increased acute coronary events (33), especially AMI. In the current study, serum endoglin levels were higher in Group 1, which included patients with poor coronary collateral development and higher rates of AMI. In addition, a negative relationship was found between serum endoglin and CRP levels as well as age. Increased age and CRP values were related to accelerated atherosclerosis (34). Our findings potentially suggest that patients with increased endoglin levels are more prone to plaque complications and AMI. In accordance with our findings, Ikemoto (11) et al. indicated that higher soluble endoglin levels were related to an increased rate of major adverse cardiac events. The relationship between poor coronary collateral vessels and higher endoglin levels might be attributable to the indirect inhibitory effect of increased endoglin levels on NO release (24); it is well known that NO plays a key role in the process of neoangiogenesis (35).

The relationship between the presence of total occlusion and coronary collateral development has been well documented (3, 19). The presence of severe stenosis in RCA and severe multi-vessel coronary stenosis were also shown to be confounding factors for coronary collateral development. The current study results also showed these variables to be confounding variables in univariate analysis, but the presence of total occlusion was a substantial marker of good collateral development (36). This suggests that total occlusion results in more ischemia as a locomotive factor for collateralization formation.

Our study had several limitations, the first of which being its sample size. Secondly, due to cost constraints, we did not investigate NO levels or important cytokines, such as TGF-β or VGF, as this would have required specialized techniques and equipment. Thirdly, we assessed coronary collateralization by Rentrop score instead of an invasive index, such as collateral flow. Using a better, invasive classification method could have further validated our findings. However, Rentrop score has been shown to be a reliable and reproducible method to evaluate coronary collateral vessels. Finally, investigation of the correlation between serum endoglin level and mortality could have also contributed to validation of our findings.

In conclusion, patients with poor coronary collaterals exhibited increased plasma endoglin levels, while decreased endoglin levels were independent markers of the presence of good coronary collateralization. Hence, endoglin levels might be promising in identifying patients with AMI and good CCC during hospitalization. Yet, further studies are needed to determine the clinical relevance of this relationship in a large population of patients with acute coronary syndrome.

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Authors' Contribution

Study concept and design: Aydin Akyuz; Acquisition of data: Aydin Akyuz, Seref Alpsoy, Dursun Cayan Akkoyun, Hasan Degirmenci, Kubilay Erselcan, and Feti Tulubas; Analysis and interpretation of data: Aydin Akyuz, Seref Alpsoy; Drafting of the manuscript: Aydin Akyuz, Seref Alpsoy; Critical revision of the manuscript for important intellectual content: Aydin Akyuz, Seref Alpsoy; Statistical analysis: Aydin Akyuz; Administrative, technical, and material support: Aydin Akyuz, Seref Alpsoy, Dursun Cayan Akkoyun, Hasan Degirmenci, Kubilay Erselcan, and Feti Tulubas; Study supervision: Aydin Akyuz, Seref Alpsoy

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