

Cyclophilin A and D Levels in Acute Coronary Syndrome and Their Relationship with Cardiovascular Risk Factors

Akut Koroner Sendromda Siklofilin A ve D Düzeyleri ve Onların Kardiyovasküler Risk Faktörleri ile İlişkisi

ABSTRACT

Objective: Our objective was to evaluate cyclophilin levels in patients with acute coronary syndrome (ACS) and their association with the clinical characteristics of these patients.

Methods: We enrolled 150 patients with ACS (n=75 ST-elevation myocardial infarction [STEMI], n = 75 non-ST-elevation myocardial infarction [NSTEMI]). For comparison, 25 healthy volunteers were included in the study. Levels of cyclophilin A, cyclophilin D, and C-reactive protein (CRP) were measured in both the acute myocardial infarction (AMI) groups and the healthy group. We examined the effects of cardiovascular risk factors, including diabetes mellitus, hypertension, dyslipidemia, age, gender, and smoking on these parameters.

Results: Cyclophilin A levels were significantly lower in the STEMI group, while cyclophilin D and CRP levels were significantly higher in all AMI groups ($P < 0.05$). A negative correlation existed between cyclophilin A and troponin T and CK-MB (respectively $r = -0.287$, $P < 0.001$; $r = -0.231$, $P = 0.005$). However, there was no correlation between cyclophilin D and the cardiac markers. A positive correlation was observed between cyclophilin D and CRP ($r = 0.219$, $P = 0.004$). Cyclophilin A was associated with hypertension, whereas cyclophilin D was associated with the female gender and dyslipidemia ($P < 0.05$).

Conclusion: Our findings suggest that a decrease in cyclophilin A indicates a more severe disease in STEMI and an increase in cyclophilin D in both STEMI and NSTEMI may be valuable markers. Therefore, further detailed studies are warranted to monitor their changes and interactions in ACS patients.

Keywords: Acute myocardial infarction, cyclophilin A, cyclophilin D

ÖZET

Amaç: Akut koroner sendromlu (AKS) hastalarda siklofilin düzeylerini ve hastaların klinik özellikleri ile ilişkisini değerlendirmeyi amaçladık.

Yöntem: AKS'li 150 hasta (n=75 STEMI, n=75 NSTEMI) çalışmaya alındı. Karşılaştırma için 25 sağlıklı gönüllü de çalışmaya dahil edildi. Akut miyokard enfarktüsü (AMI) gruplarında ve sağlıklı grupta siklofilin A, siklofilin D ve CRP düzeyleri ölçüldü. Diabetes mellitus, hipertansiyon, dislipidemi, yaş, cinsiyet ve sigara içme gibi kardiyovasküler risk faktörlerinin bu parametreler üzerindeki etkisi incelendi.

Bulgular: Siklofilin A düzeyleri STEMI grubunda anlamlı olarak düşük, siklofilin D ve CRP düzeyleri tüm AMI gruplarında anlamlı olarak yüksekti ($P < 0,05$). Siklofilin A ile troponin T ve CK-MB arasında negatif korelasyon bulunurken (sırasıyla $r = -0,287$, $P < 0,001$, $r = -0,231$, $P = 0,005$), Siklofilin D ile kardiyak belirteçler arasında korelasyon saptanmadı. Siklofilin D ile CRP arasında pozitif korelasyon vardı ($r = 0,219$, $P = 0,004$). Siklofilin A hipertansiyon ile, Siklofilin D ise kadın cinsiyet ve dislipidemi ile ilişkili bulundu ($P < 0,05$).

Sonuç: Bu çalışma, STEMI'de daha şiddetli hastalık için azalmış siklofilin A'nın ve hem STEMI hem de NSTEMI'de artmış siklofilin D'nin değerli belirteçler olabileceğini düşündürmektedir. Bu nedenle, AKS hastalarında değişimlerini ve etkileşimlerini izlemek için daha ayrıntılı çalışmalar yapılmalıdır.

Anahtar Kelimeler: Akut miyokard enfarktüsü, siklofilin A, siklofilin D

ORIGINAL ARTICLE

KLİNİK ÇALIŞMA

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Cyclophilins are proteins that belong to the immunophilin family and possess peptidyl-prolyl cis-trans isomerase (PPIase) activity.¹ Sixteen cyclophilin proteins exist in humans, and seven of them are recognized as major cyclophilins. These proteins are situated in different cell compartments and participate in several processes, including the formation of peptide bonds, intracellular communication, apoptosis, and immune system regulation.²

Cyclophilin A, the first identified PPIase and the most prevalent cyclophilin in our body, is secreted into the cell's cytoplasm in response to an inflammatory stimulus. It acts as a chemoattractant for inflammatory cells and can cause damage to endothelial cells and promote vascular smooth muscle cell proliferation.³ In the process of atherosclerosis, cyclophilin A is released into the plasma due to inflammation. This causes an acceleration in the atherosclerotic process by inducing further inflammation and vascular remodeling. It also increases the intake of low-density lipoprotein cholesterol (LDL-C) into the vascular wall due to an increase in adhesion molecules and scavenger receptors.⁴

Cyclophilin D is another cyclophilin located in the mitochondrial matrix of the cell. It is associated with the opening of the mitochondrial permeability transition pore (mPTP) and plays a role in mitochondrial calcium regulation and apoptosis. An increase in mitochondrial calcium levels during ischemia and an increase in reactive oxygen species during reperfusion cause the mPTP to open in acute coronary syndrome (ACS). Depending on the duration of this process, cell damage and cell death can occur.⁵

Few studies have examined serum levels of both cyclophilin A and cyclophilin D in patients with acute myocardial infarction (AMI).⁶ The primary aim of this study was to investigate the concentrations of both cyclophilin A and D in patients with ST-elevation myocardial infarction (STEMI) or non-ST-elevation myocardial infarction (NSTEMI). We also evaluated the relationship between cyclophilin levels and risk factors for coronary syndromes.

Materials and Methods

Subjects

The study included 150 patients (75 NSTEMI, 75 STEMI) who were admitted to Zonguldak Bülent Ecevit University Hospital Emergency Service between December 2018 and December 2019 with AMI signs and symptoms. AMI was diagnosed based on typical chest pain, serial electrocardiogram (ECG) evaluations,

serum troponin T and Creatine Kinase-Myocardial Band (CK-MB) levels, and coronary angiography. AMI patients were classified as either STEMI or NSTEMI based on their ECG results.⁷ The medical history of patients was evaluated upon admission, and those with congenital heart disease or cancer were excluded from the study. Data were recorded on cardiovascular risk factors, including age, gender, smoking, diabetes mellitus, dyslipidemia, and hypertension. Diabetes mellitus (DM) was defined by fasting glucose levels ≥ 126 mg/dL, an HbA1c value $\geq 6.5\%$, or any treatment for DM.⁸ An LDL-C level ≥ 130 mg/dL and/or high-density lipoprotein cholesterol (HDL-C) level < 40 mg/dL was considered indicative of dyslipidemia.⁹ Hypertension was defined as a blood pressure exceeding 140/90 mmHg or the use of an antihypertensive drug.¹⁰ The use of lipid-lowering drugs and antiaggregant/anticoagulant medications was also documented.

For comparison, 25 healthy volunteers who visited an outpatient clinic for health check-ups were included in the study. These subjects had no chronic diseases, acute or chronic infections, or were on any medications. All procedures performed in this study involving human participants adhered to the ethical standards of both the institutional and/or national research committees, as well as the 1964 Helsinki declaration and its subsequent amendments or comparable ethical standards. This study received approval from the Ethics Committee of Zonguldak Bülent Ecevit University Hospital (Approval Number: 05.12.2018-2018/23, Date: 05.12.2018). All participants were informed about the research, and the "Minimum Informed Volunteer Consent Form" was read to them. Both verbal and written consents were obtained.

Sample Analysis

Blood samples from the patients were collected upon their initial admission to the hospital during the diagnostic evaluation for ACS. After clotting, gel-separator blood tubes were centrifuged at 3500 rpm for 10 minutes to obtain serum. Levels of troponin T, CK-MB, total cholesterol (TC), HDL-C, LDL-C, and triglycerides (TG) were analyzed as routine. The serum was separated and stored at -80°C for subsequent analysis.

Serum TC, TG, HDL-C, and LDL-C levels were measured using the enzymatic colorimetric method (Roche Cobas c501, Germany). Serum troponin T and CK-MB levels were determined using the electrochemiluminescence method (Roche Cobas e411, Germany). The intra-assay coefficient of variations (CVs) for the TC, TG, HDL-C, and LDL-C kits were $< 1\%$, and their inter-assay CVs were $< 3\%$. The intra-assay CVs for the troponin T and CK-MB kits were $< 3\%$, and their inter-assay CVs were $< 4\%$.

We also analyzed the levels of cyclophilin A, cyclophilin D, and C-reactive protein (CRP) in the stored serum. Concentrations of cyclophilin A, cyclophilin D, and CRP were determined using a sandwich enzyme-linked immunosorbent assay with commercially available kits (Shanghai YL Biotech Co. Ltd, Shanghai, China). The sensitivities for the cyclophilin A and D kits were 0.49 and 0.119 ng/mL, respectively, and their detection limits were 1.25 and 0.156 ng/mL, respectively. The intra-assay CVs for these kits were $< 10\%$ and the inter-assay CVs were $< 12\%$. The CRP kit had a sensitivity of 0.012 mg/L, a detection limit of 0.2 mg/L, and intra-assay CV of $< 8\%$, and an inter-assay CV of $< 10\%$.

ABBREVIATIONS

ACS	Acute coronary syndrome
AMI	Acute myocardial infarction
CRP	C-reactive protein
DM	Diabetes mellitus
ECG	Electrocardiogram
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
mPTP	Mitochondrial permeability transition pore
NSTEMI	Non-ST-elevation myocardial infarction
PPIase	Peptidyl-prolyl cis-trans isomerase
STEMI	ST-elevation myocardial infarction
TC	Total cholesterol
TG	Triglyceride

Statistical Analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS®) software version 19 (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was used to assess the normal distribution of numerical variables. Descriptive statistics for numerical variables were presented as mean \pm standard deviation and median (min-max), and for verbal data as numbers and percentages. For comparing two groups in terms of numerical variables, the student t-test was used for parametric variables, while the Mann-Whitney U test was applied for non-parametric variables. The Kruskal-Wallis variance analysis was employed to compare three or more groups for numerical variables. Comparison of subgroups in pairs was conducted using Dunn's test within the Kruskal-Wallis variance analysis. Pearson Chi-square, Yates Chi-square, and Fisher's Exact Chi-square tests were used to compare groups for verbal variables. The linear relationship between two numerical variables was examined using Pearson correlation analysis for parametric variables and Spearman correlation for non-parametric variables. Binary Logistic Regression Analysis was employed to identify risk factors, and $P < 0.05$ was considered significant for all assessments.

Results

Baseline Characteristics

Baseline characteristics of subjects who participated in our study are displayed in Table 1. Age and sex distributions exhibited

no significant difference between the AMI and control groups. Notable statistically significant differences between the AMI and control groups are in CK-MB, troponin T, CRP, and HDL-C levels. The distribution of cardiovascular risk factors among AMI patients is also detailed in the table.

Comparisons of Parameters

Figure 1 (1A, 1B, and 1C) showcases the comparison of cyclophilin A, D, and CRP levels between all patients and the control group, as well as between AMI patient subgroups (STEMI and NSTEMI). Cyclophilin A levels were lower in all AMI patients (median 5.2 ng/mL, min-max: 1.25-29.7 ng/mL) compared to controls (median 6.7 ng/mL, min-max: 1.9-9.1 ng/mL; $P = 0.029$). In subgroup analysis, cyclophilin A levels in STEMI patients (median 2.8 ng/mL, min-max: 1.25-29.7 ng/mL) were significantly lower than in NSTEMI patients (median 7.0 ng/mL, min-max: 1.25-24.1 ng/mL, $P < 0.001$). Cyclophilin D levels were significantly higher in AMI patients (median 0.76 ng/mL, min-max: 0.56-1.48 ng/mL) than in controls (median 0.65 ng/mL, min-max: 0.55-0.99 ng/mL, $P = 0.002$). No difference was observed in cyclophilin D levels between STEMI (median 0.75 ng/mL, min-max: 0.57-1.45 ng/mL) and NSTEMI (median 0.76 ng/mL, min-max: 0.56-1.48 ng/mL) groups ($P = 0.693$). CRP levels were higher in all AMI patients (median 11.9 mg/L, min-max: 0.60-247 mg/L) compared to controls (median 3.0 mg/L, min-max: 0.30-5.96 mg/L; $P < 0.001$). There was no significant difference in CRP levels between STEMI (median 17.2 mg/L,

Table 1. Baseline Characteristics of Subjects

Characteristic	AMI (n = 150)	Control (n = 25)	P
Male (%)	74.7	76.0	1.000
Age (years)	60.7 \pm 8.2	60.9 \pm 5.4	0.880
CK-MB (ng/mL)	32.4 0.99-300	1.25 0.3-3.29	< 0.001
Troponin (ng/mL)	0.99 0.02-10.0	0.02 0.003-0.04	< 0.001
CRP (mg/L)	11.90 0.60-247.60	3.00 0.30-5.96	< 0.001
HDL-C (mg/dL)	37 22-64	44 30-98	< 0.001
LDL-C (mg/dL)	106 39-230	100 54-131	0.410
TC (mg/dL)	175 95-325	177 112-221	0.886
TG (mg/dL)	146 243-681	143 87-243	0.555
Smoking (%)	30.7	20	0.396
Hypertension (%)	42	-	-
Diabetes mellitus (%)	39.3	-	-
Dyslipidemia (%)	76.7	-	-
Anticoagulant/antiplatelet (%)	26.7	-	-
Statin (%)	7.3	-	-

AMI, acute myocardial infarction; CK-MB, Creatine kinase-MB; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

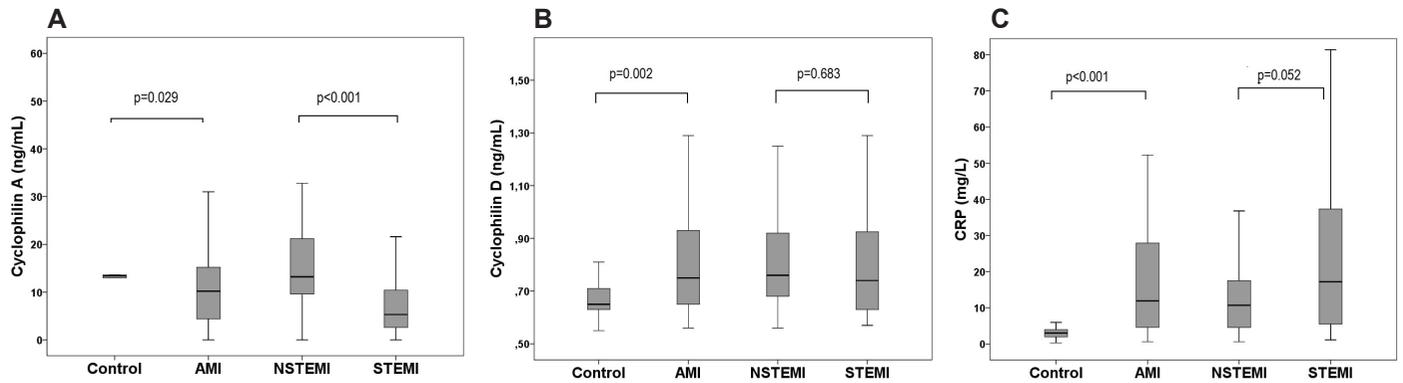


Figure 1. Comparison of Cyclophilin A (A), D (B), and CRP (C) levels between all AMI patients, AMI subgroups (STEMI and NSTEMI), and control.

Table 2. The Relationship of Cyclophilins with Cardiovascular Risk Factors

Risk Factors	Cyclophilin A		Cyclophilin D	
	Mean ± SD	P	Mean ± SD	P
Age				
50<	7.3 ± 4.47	0.579	0.81 ± 0.22	0.960
50>	6.75 ± 5.81		0.80 ± 0.20	
Gender				
Female	6.18 ± 4.60	0.343	0.84 ± 0.24	0.023*
Male	7.01 ± 5.99		0.79 ± 0.19	
Smoking				
Yes	6.21 ± 4.19	0.421	0.77 ± 0.16	0.026*
No	7.06 ± 6.21		0.81 ± 0.22	
DM				
Yes	6.44 ± 5.30	0.679	0.84 ± 0.22	0.200
No	7.01 ± 5.90		0.78 ± 0.19	
Hypertension				
Yes	7.82 ± 6.89	0.005*	0.82 ± 0.22	0.709
No	6.19 ± 4.69		0.79 ± 0.19	
Dyslipidemia				
Yes	6.94 ± 5.96	0.650	0.81 ± 0.22	0.043*
No	6.46 ± 4.90		0.79 ± 0.16	

Data are expressed as mean ± SD.

min-max: 1.11-247 mg/L) and NSTEMI (median 10.7 mg/L, min-max: 0.60-157 mg/L) groups ($P = 0.052$).

There was a negative correlation between cyclophilin A and troponin T ($r = -0.287, P < 0.001$), and CK-MB ($r = -0.231, P = 0.005$) in all AMI patients. These correlations were not observed solely in STEMI or NSTEMI groups for troponin T (respectively, $r = -0.03, P = 0.807$; $r = 0.03, P = 0.801$) and for CK-MB (respectively, $r = 0.12, P = 0.320$; $r = 0.14, P = 0.235$). Conversely, no correlation was detected between cyclophilin D and troponin T ($r = 0.161, P = 0.116$), and CK-MB ($r = 0.162, P = 0.132$). However, a positive correlation between cyclophilin D and CRP was observed ($r = 0.219, P = 0.004$).

The Relationship with Cardiovascular Risk Factors

The relationship between cyclophilin levels and cardiovascular risk variables in AMI patients is detailed in Table 2. Cyclophilin A was significantly increased in patients with hypertension. However, it showed no association with risk factors like smoking, gender, advanced age (≥ 50 years), DM, and dyslipidemia. With regard to the type of AMI, the influence of hypertension was more pronounced in STEMI patients ($P = 0.09$), although it was not statistically significant.

Cyclophilin D was significantly elevated in patients with dyslipidemia and in females, but was notably decreased in smokers. Additionally, advanced age (≥ 50 years), hypertension, and DM did not significantly impact cyclophilin D levels.

Discussion

In our study, we observed decreased cyclophilin A levels in AMI patients, especially in the STEMI group, compared to healthy volunteers. STEMI, being more severe than NSTEMI, is typically linked to a worse prognosis.¹¹ Notably, a negative correlation was found between cyclophilin A and cardiac markers (troponin T and CK-MB), indicating the disease's severity.

These findings contradict previous research on cyclophilin A levels in ACS patients. Yan et al.¹² examined serum cyclophilin A levels in 60 stable angina patients, 60 with unstable angina, 90 with AMI, and 50 healthy volunteers. They demonstrated that cyclophilin A levels were significantly higher in AMI and unstable angina patients than in healthy volunteers and those with stable angina. In another study, cyclophilin levels were analyzed in 320 patients presenting with chest pain and ischemia findings on exertional ECG or myocardial perfusion radiography, undergoing their first coronary angiography.¹³ In this study, where occlusion of at least 51% of the vessel lumen was considered significant stenosis, cyclophilin A levels increased in proportion to the number of stenotic vessels. In contrast to these studies, one study reported significantly lower cyclophilin A levels in AMI patients, similar to our findings. They also noted significantly higher cyclophilin A levels in hypertensive patients compared to normotensive ones, mirroring our study.¹⁴ Results of our study suggest that in STEMI patients, as damage severity, tissue necrosis, and cell death increase, cyclophilin A levels decrease. Illustrating the relationship between cyclophilin A and troponin in this study enriches the literature, as this connection had not been previously explored.

Cyclophilin D serves as a pharmacological target to reduce ischemia-reperfusion injury in various animal models.^{15,16} Some researchers have determined that inhibiting cyclophilin D offered maximal protection and resulted in a smaller infarct area three hours after reperfusion.¹⁷ The impact of cyclophilin D inhibition was assessed in 58 STEMI patients admitted within 12 hours of their initial chest pain. Treatment with cyclosporine, which inhibits cyclophilin D, led to a significant drop in creatine kinase (CK) levels in these patients. However, there was no notable effect on troponin I levels. Additionally, the infarct area was markedly smaller in patients treated with cyclophilin D inhibition than in the control group.¹⁸ Contrarily, an earlier report found no differences in blood levels of cyclophilin D between coronary artery disease patients and healthy volunteers.⁶ We are the first to demonstrate that serum cyclophilin D levels are increased in AMI patients, irrespective of STEMI or NSTEMI diagnosis. The significant positive correlation between cyclophilin D and CRP implies an inflammation-induced increase. It should be emphasized that being female and having dyslipidemia both contribute to increased levels of cyclophilin D.

The study had several limitations. First, the small sample size limited the power of the tests, but the study still offered valuable insights to the literature. Second, we did not identify the cardiovascular risk profile of the healthy group. Third, we were unable to gather prognostic information about the patients.

In conclusion, this study suggests that decreased cyclophilin A levels in cases of more severe STEMI, and increased cyclophilin

D levels in both STEMI and NSTEMI, may serve as significant markers. Hence, more detailed studies should be conducted to observe their variations and interactions in ACS patients.

Ethics Committee Approval: The study was approved by the Ethics Committee of Zonguldak Bülent Ecevit University Hospital (Approval Number: 2018/23, Date: 05.12.2018).

Informed Consent: All participants were informed about the research, and the "Minimum Informed Volunteer Consent Form" was read to them. Both verbal and written consents were obtained.

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Conflict of Interests: The authors confirm that they have no competing interests.

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