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Research Article

Paraoxonase 1 gene polymorphısms (Q192r and L55m) and associatıon wıth coronary slow flow

Paraoksonaz 1 gen polimorfizmleri (Q192r ve L55m) ve koroner yavaş akımla ilişkisi

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Abstract

Aim: Coronary slow flow (CSF) is an angiographic entity characterized by slow progression of opaque material and an early indicator of atherosclerosis. Paraoxonase 1 (PON1) protects high-density lipoprotein (HDL) and low-density lipoprotein (LDL) from oxidative modifications. PON 1 has two amino acid polymorphisms (192Q/R and 55L/M) and that affect its functioning. We aim to determine PON1 two genetic polymorphisms and relationship with CSF. As we know, our study is the first to assessment the relationship PON1 gene polymorphisms (L55M and Q192R) and CSF.

Material and Methods: We included a total of 100 patients and 2 groups as normal coronary flow (NCF) and CSF. Genomic sequences of rs854560 and rs662 polymorphisms were determined using polymerase chain reaction. The research protocol was approved by Fırat University Institutional Review Board (Approval No:16).

Results: The mean age of CSF group was 45.4±17 and NCF group was 50.5±11 years. There was the statistically difference in terms of the frequency of carrying Q and R alleles. For dual genotypes, the QQLM genotype was more common in CSF group, whereas the QRLM genotype was more common in NCF. Significant differences were found between patients with QQLM, RRLL, RRLM and QRLM genotypes and healthy individuals.

Conslusion: We found a significant relationship between the Q allele and the QQLM genotype and CSF, and we thought that these may be risk factors for CSF. In addition, the fact that the R allele and QRLM, RRLL, and RRLM genotypes were higher in the NCF group and there was a statistically significant relationship suggested that these might be protective factors for CSF.

Keywords: coronary slow flow; paraoxonase; gene polymorphism; antioxidant

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Öz

Amaç: Koroner yavaş akım (KYA), opak maddenin yavaş ilerlemesi ile karakterize anjiyografik bir antitedir ve aynı zamanda ve aterosklerozun erken bir göstergesi olduğu düşünülmektedir. İnsan paraoksonazı 1 (PON1), yüksek yoğunluklu lipoproteini (HDL) ve düşük yoğunluklu lipoproteini (LDL) oksidatif modifikasyonlardan korur. Paraoksonaz 1'in işleyişini etkileyen iki amino asit polimorfizmi (192Q/R ve 55L/M) vardır. PON1 iki genetik polimorfizmi ve koroner yavaş akım ile ilişkisini belirlemeyi amaçlıyoruz. Bildiğimiz kadarıyla çalışmamız PON1 gen polimorfizmleri (L55M ve Q192R) ile KYA ilişkisini değerlendiren ilk çalışmadır.

Gereç ve Yöntemler: Çalışmaya toplam 100 hasta dahil edildi ve normal koroner akım (NKA) ve KYA olmak üzere 2 gruba ayrıldı. rs854560 ve rs662 polimorfizmlerinin genomik dizileri polimeraz zincir reaksiyonu kullanılarak belirlendi. Araştırma protokolü Fırat Üniversitesi Kurumsal İnceleme Kurulu tarafından onaylanmıştır (Onay No:16).

Bulgular: Koroner yavaş akım grubunun yaş ortalaması 45,4±17 ve NKA grubunun 50,5±11 idi. Q ve R alellerini taşıma sıklığı açısından istatistiksel olarak fark vardı. Dual genotipler için, QQLM genotipi KYA grubunda daha yaygınken, QRLM genotipi NKA'de daha yaygındı. QQLM, RRLL, RRLM ve QRLM genotiplerine sahip hastalar ile sağlıklı bireyler arasında anlamlı fark bulundu.

Sonuçlar: Q aleli ile QQLM genotipi ve KYA arasında anlamlı bir ilişki bulduk ve bunların KYA için risk faktörleri olabileceğini düşündük. Ayrıca R aleli ile QRLM, RRLL ve RRLM genotiplerinin NKA grubunda daha yüksek olması ve istatistiksel olarak anlamlı bir ilişki bulunması bunların KYA için koruyucu faktörler olabileceğini düşündürdü.

Anahtar Kelimeler: koroner yavaş akım, paraoksonaz, gen polimorfizmi, antioksidan

Introduction

Genetic factors contribute to the risk of coronary artery disease (CAD) almost as much as environmental factors. Examining populations (patient–control) by genotyping common single-nucleotide polymorphisms within a suspected gene and its regulatory sequences is essential and provides new insights into the genetic pathways of the disease [1].

Coronary slow flow (CSF) is an important, angiographic entity characterized by the slow progression of opaque material and delayed coronary opacification without coronary artery ischemic provocative maneuvers in normal or near-normal coronary angiography. CSF was first described by Tambe et al. in 1972 and has been reported in 1–4% of patients who have undergone coronary angiography [2,3].

CSF is associated with arrhythmias, recurrent angina, and unnecessary interventions or hospitalizations. It is also thought to be an early indicator of atherosclerosis [4,5]. Pathophysiological factors, such as microvascular dysfunction, endothelial/vasomotor dysfunction, small vessel diseases, and inflammatory/neurohormonal imbalance were related to CSF. Despite all this, the underlying causes have not been precisely identified [3,6,7].

The paraoxonase gene family has three members--PON1, 2, and 3-- and is localized between q21.3 and q22.1 on the long arm of chromosome 7 [8]. Serum paraoxonase 1 (PON1) is one of the genes that plays an important role in vascular pathology and is thus considered a biomarker of CAD. Serum PON1 protects high-density lipoprotein (HDL) and low-density lipoprotein (LDL) from oxidative modification. The antioxidant activity of HDL is largely due to PON, which has the ability to metabolize lipid peroxides. Previous studies and meta-analyses have shown an association between PON1 polymorphisms and CAD [9,10].

PON1 has two amino acid polymorphisms. One is the substitution of methionine and leucine (M/L) amino acids in the 55th position, and the other is the substitution of arginine and glutamine (Q/R) amino acids at position 192 [8].

Based on the above studies and meta-analyses, we hypothesized that PON1 gene mutations might influence coronary blood flow and compared two polymorphisms of the PON1 gene in patients with CSF and normal coronary flow (NCF).

Material and Methods

This study was performed at the Cardiology Clinic of Fırat University Hospital. We included 100 patients aged 18 years or older who presented with complaints of chest pain and had undergone coronary angiography (CAG). Fifty patients with NCF served as the control group, and 50 patients with CSF served as the patient group.

Our exclusion criteria were acute coronary syndrome, unstable angina pectoris, heart failure (ejection fraction < 50%), significant valvular heart disease, and prior coronary artery bypass graft surgery. CSF was diagnosed by the joint decision of two experienced invasive cardiologists. We defined obstructive CAD as the presence of at least one major epicardial coronary artery with 40% or more stenosis.

Written informed consent was obtained from the patients for this study and is documented at our department records.

The research protocol was approved by Fırat University Institutional Review Board (Approval No:16). This study was conducted in agreement with the Declaration of Helsinki-Ethical principle for medical research involving human subjects.

Evaluation of Coronary Blood Flow

Coronary angiographies were performed using the standard Judkins technique with a 6F catheter. The Thrombolysis in Myocardial Infarction (TIMI) frame count (TFC) method was used for the quantitative measurement of coronary blood flow.

The first frame is when the contrast material fully opacifies the origin of the artery and starts to progress. The last frame is defined separately for each coronary artery: the distal mustache (whale's tail) for left anterior descending (LAD), the distal bifurcation of the longest branch for circumflex artery (Cx), and the emergence of the first posterolateral branch for the right coronary artery (RCA).

The normal frame counts for LAD artery are 1.7 times greater than CX and RCA.

We obtained the corrected TIMI frame count by dividing the LAD frame value 1.7.

36.2±2.6 for LAD; 22.2±4.1 for Cx; Patients with at least one coronary artery with a frame count above 20.4±3.0 for RCA were defined as CSA. For clinical practicality, the number of frames over 40 for LAD, over 25 for Cx, and over 24 for RCA were taken as coronary slow flow.

Genetic Analyses

Blood samples (5 mL) were collected in the ethylenediamine tetraacetic acid (EDTA) tubes for each patient. Genomic deoxyribonucleic acid (DNA) concentration and purity were determined by ultraviolet (UV) spectrophotometer. The absorbance ratio of a pure DNA sample at 260 nm and 280 nm was 1.8. The patient and control group DNA samples were measured, and their concentrations and purity were determined. DNA samples with values not close to 1.8 were re-isolated.

PON1 genes with rs854560 and rs662 polymorphisms were studied using the Fast Real-Time System (Applied Biosystems, Foster City, CA, USA) using TaqMan probes.

M55L: The genomic sequence of the rs854560 polymorphism is like GCCAGTCCATTAGGCAGTATCTCCA(A/T)GTCTTCAGAGCCAGTTTCTGCCCAGA. In this polymorphisym, the A-to-T transversion (ATG codon --> TTG codon), results the substitution of methionine (the 55th amino acid) by leucine.

Q192R: The genomic sequence of the Rs662 polymorphism is like TAAACCCAAATACATCTCCCAGGAT(C/T)GTAAGTAGGGGTCAAGAAAATAGTG. In these polymorphisms, the C-to-T transversion (CAA codon CGA codon) results in the substitution of glutamine (the 192nd amino acid) by arginine.

The genomic sequences of rs854560 and rs662 polymorphisms were determined using polymerase chain reaction (PCR).

After PCR, the homozygous mutant, heterozygous normal, and homozygous normal genotypes were determined according to allele 1 and allele 2 differentiation.

Statistical Analysis

Statistical evaluation was performed using the SPSS program. The relationships between the parameters were evaluated using Pearson's correlation analysis. The distribution of the patient and control groups, genotype, and allele frequencies were achieved using chi-square analysis. The Mann–Whitney U test, which is a non-parametric test, was used to evaluate the differences between the groups. P values of < 0.05 were considered statistically significant in the evaluations.

Results

The demographic and clinical characteristics of the study cohort are shown in Table 1. The mean age of the NCF group was 45.4 ± 17 years, and the mean age of the CSF group was 50.5 ± 11 years. CSF occurred more frequently in males (50% vs. 58%), but this result was not statistically significant.

Table 1. Study population baseline characteristics

Variables	CSF group (n=50)	NCF group (n=50)	p
Age (years)	50.5±11	45.4±17	0.91
Gender, male (n, %)	21 (58)	25 (50)	0.55
Diabetes mellitus (n, %)	11 (22)	4 (8)	0.51
Hypertension (n, %)	31 (62)	14 (28)	0.001**
LDL-C (mg/dL) (mean, SD)	110±36	100±22	0.09

CSF: Coronary slow flow, NCF: normal coronary flow, LDL-C, low-density lipoprotein cholesterol, **= p<0.05 (statically significant)

The number of diabetic and hypertension patients in the CSF group was higher than in the control group. This difference was not statistically significant in the diabetic patients.

In our study, 44% of all participants were hypertensive. Hypertension was detected in 62% of the CSF group, and a statistically significant difference was observed compared to the NCF group (p = 0.001). In this respect, hypertension can be considered a risk factor for or predictor of CSF. However, there was no statistically significant difference between the PON1 L55M-Q192R genotypes and hypertension in either group. Also, we did not aim to investigate the relationship between diabetes, hypertension, and CSF in our study.

In the CSF group, the mean TFC values were calculated as 46.3 ± 11.3 for LAD, 35.2 ± 15.03 for Cx, and 24.6 ± 9.55 for RCA.

PON1-55 rs854560 L/M Polymorphism Distributions in CSF and NCF Groups

There was no significant difference between the CSF and NCF groups in terms of PON1 genotype distribution and frequency or PON1 allele distribution and frequency (p = 0.7 and p = 0.8, respectively; Table 2). The genotype distribution for L55M in the NCF group was 52% for LM, 36% for LL, and 12% for MM. We found that the least common genotype was MM, and the most common genotype was LM. Our results are in line with an earlier Turkish study conducted on the L55M genotype [11].

PON1-192 rs662 Q/R Polymorphism Distributions in CSF and NCF Groups

There was no significant difference between the CSF and NCF groups in terms of PON1 genotype distribution and frequency (p = 0.53). A statistically significant difference was found between the two groups in terms of PON1 allele distribution and frequency (p = 0.012; Table 3).

In the CSF group, the QQ, QR, and RR genotype frequencies were 62%, 34%, and 4%, respectively; in the NCF group, the same frequencies were 42%, 40%, and 18%, respectively. The genotype distribution for Q192R was 42% (QQ), 40% (QR), and 18% (RR). Our results are in line with an earlier Turkish study conducted on the Q192R genotype [12]. The QQ genotype was common in both the CSF and NCF groups, and the difference was not statistically significant.

Dual Genotype Frequencies

A statistically significant difference was found between the CSF and the NCF groups in the evaluation of dual genotypes.

For the PON1 gene L55M and Q192R loci, the QQLM genotype was more common in the CSF group, whereas the QRLM genotype was more common in the NCF group.

Statistically significant differences were found between the CSF and the NCF groups regarding the QQLM (p = 0.06), RRLL (p = 0.001), RRLM (p = 0.041), and QRLM (p = 0.001) genotypes.

The QQLM genotype was the most common (40%) genotype in the CSF group. There was a significant difference between the CSF and the NCF groups in terms of the QQLM genotype, and the QRLM genotype was the most common (30%) genotype in the NCF group. There was also a significant difference between the CSF and the NCF groups in terms of the QRLM genotype. Additionally, no individuals were found in the RRMM genotypes (Table 4).

Frequencies of at Least One Q, R, L, and M Allele

We compared the frequencies of carrying at least one Q, R, L, or M allele. There was no statistically significant difference between the CSF and NCF groups in terms of the frequency of carrying the L and M alleles (approximately p = 0.05). However, we found a statistically significant difference in terms of the frequency of carrying the Q and R alleles (p = 0.001; Table 5).

The frequency of the Q allele was higher in the CSF group and was found to be statistically significant. In another study, a significant difference was found between the CAD and control groups in terms of Q allele carriage and frequency (78%) [13]. We thought that the presence of Q allele might be a risk factor for CSF and for early atherosclerosis. The L allele carriage frequency was high in the control group, but it was not statistically significant.

In terms of age, gender, hypertension, diabetes, and LDL, and considering the significant demographic characteristics of patients and relationship with the PON1 gene L55M and Q192R genotypes, no statistically significant difference was found between the CFA and NCF groups for the PON1 gene L55M and Q192R genotypes (p>0.05).

Table 2. PON1 L55M genotype and allele distribution and frequencies

Genotype Distribution and Frequencies	LL	LM	MM	Odds	Odds Ratio	CI %95	p
CSF (n=50)	18 (%36)	27 (%54)	5 (%10)	1.4	1.04	0.22-2.95	-
NCF (n=50)	18 (%36)	26 (%52)	6 (%12)	1.3			-
Allele Distribution and Frequencies	L	M					
CSF (n=50)	41 (0.82)	59 (1.18)					-
NCF (n=50)	42 (0.84)	58 (1.16)					-

- = p>0.05, CSF: Coronary slow flow, NCF: normal coronary flow

Table 3. PON1 Q192R genotype and allele distribution and frequencies

Genotype Distribution and Frequencies	QQ	QR	RR	Odds	Odds Ratio	CI %95	p
CSF (n=50)	31 (%62)	17 (%34)	2 (%4)	3.7	6.8	0.25-1.35	0.5
NCF (n=50)	21 (%42)	20 (%40)	9 (%18)	0.5			
Allele Distribution and Frequencies	Q	R					
CSF (n=50)	79 (1.58)	21 (0.42)					0.012**
NCF (n=50)	62 (1.24)	38 (1.9)					

**= p<0.05 (statically significant), CSF: Coronary slow flow, NCF:normal coronary flow

Table 4. Distribution of PON1 Q192R and PON1 L55M genotype frequencies in CSF and NCF groups

Dual genotype		CSF group (%)	NCF group (%)	p
QQ	LL	14	12	0.06
	LM	40	18	0.001**
	MM	8	12	0.3
RR	LL	4	17	0.001**
	LM	-	4	0.041**
	MM	-	-	-
QR	LL	18	10	0.7
	LM	14	30	0.001**
	MM	2	-	0.1

**= p<0.05 (statically significant), CSF: Coronary slow flow, NCF:normal coronary flow

Table 5. Frequency of at least one Q, R, L and M allele

	CSF group (%)	NCF group (%)	p
L	90	88	0.7
M	64	64	0.1
Q	96	52	0.001**
R	38	58	0.001**

**= p<0.05 (statically significant), CSF: Coronary slow flow NCF: normal coronary flow

Discussion

CSF is defined as delayed opacification of the coronary vasculature at the distal level. The pathophysiological mechanisms of CSF have not been elucidated, and it has been considered an early stage of CAD [14,15].

In cases with CSF, it has been observed using the intravascular ultrasound-IVUS- technique that the coronary arteries of these patients are not normal. On the contrary, it was showed diffuse intimal thickening, calcification, and atheroma that does not lead to luminal stenosis in the coronary arteries [16].

PON1 is located on HDL in serum and metabolizes lipid peroxides, which play a role in protecting against the accumulation of LDL and atherosclerosis. Genetic variations in the PON1 gene may affect this ability [17,18].

Several studies have shown the role of PON genes in the escalating risk of CAD (19,20). In addition, some previous studies have extensively examined the Q192R and L55M polymorphisms in PON1 in different populations [21–23].

Karakaya et al. examined the relationship between serum paraoxonase activity, phenotype distribution, and lipoproteins in patients with CAD. They found no significant difference in terms of paraoxonase genotype distribution, but they showed that low paraoxonase activity could be a risk factor for CAD [24].

Aynacıoğlu et al. showed that there was no significant relationship between PON1-Q192R polymorphism and CAD in a Turkish population [25].

Similarly, Kaman et al. could not find a significant relationship between the Q192R polymorphism and CAD in their study. However, they found a significant relationship between L55M polymorphism and CAD [11].

Our study is the first to assess the relationship between PON1 gene mutations (L55M and Q192R) and CSF. Previous studies have investigated the relationship between PON1 activity and CSF or between PON1 mutations and CAD [26,27].

In our study, the QQLM genotype was higher in the CSF group, and the difference between the two groups was significant, which suggests that the QQLM genotype may be a risk factor for CSF.

The QRLM, RRLM, and RRLL genotypes were more common in the NCF group, and the difference was statistically significant for all three groups. This suggests that the QRLM, RRLM, and RRLL genotypes may be protective factors in the case of CSF.

In our study, we found a significant relationship between the Q allele, the QQLM genotype, and CSF. We hypothesize that these may be risk factors for CSF. In addition, the fact that the R allele and the QRLM, RRLL, and RRLM genotypes were higher in the NCF group than in the CSF group and that there was a statistically significant relationship suggested that these might be protective factors in the case of CSF.

Our study was a single-center study, and the study population

was relatively small. Despite these limitations, our results are significant due to their contribution as the first study to evaluate the relationship between PON1 polymorphisms and CSF. Nevertheless, large randomized controlled studies are needed to represent this population.

Conclusion

The PON1 gene plays an important protective role in CAD and CSF. L55M and Q192R polymorphisms, which have an important place in PON1 activity, should be clarified with large-scale studies.

Pharmacological interventions that regulate PON1 activity or gene expression may play an important role in the prevention of CAD.

The authors declared that the content of the manuscript has not been presented before in any meeting. The authors have no conflicts of interest to declared.

References

1. McPherson R, Tybjaerg-Hansen A. Genetics of coronary artery disease. Circ res. 2016;118(4):564-578.
2. Hawkins BM, Stavrakis S, Rousan TA, Abu-Fadel M, Schechter E. Coronary slow flow-prevalence and clinical correlations. Circ J. 2012;76(4):936-942.
3. Tambe AA, Demany MA, Zimmerman HA, Mascarenhas E. Angina pectoris and slow flow velocity of dye in coronary arteries- A new angiografic finding. Am Heart J. 1972;84(1):66-7.
4. Türkoğlu C, Şeker T, Genç Ö, Yıldırım A, Topuz M. The relationship between H2FPEF score and coronary slow flow phenomenon. Turk Kardiyol Dern Ars. 2022;50(4):242-249.
5. Wang X, Nie SP. The coronary slow flow phenomenon: characteristics, mechanisms and implications. Cardiovasc Diagn Ther. 2011;1(1):37-43.
6. Kurtoğlu N, Akcay A, Dindar I. Usefulness of oral dipyridamole therapy for angiographic slow coronary artery flow. Am J Cardiol. 2001; 87(6):777-779.
7. Beltrame JF, Limaye SB, Wuttke RD, Horowitz JD. Coronary hemodynamic and metabolic studies of the coronary slow flow phenomenon. Am Heart J. 2003;146(1):84-90.
8. Primo-Parma SL, Sorenson RC, Teiber J, La Du BN. The Human serum Paraoxonase/arylesterase gene (PON1) is one member of a multigene family. Genomic. 1996;33(3):498-509.
9. Yazmín HD, Tovilla-Zarate CA, Juárez-Rojop IE et al. Effects of paraoxonase 1 gene polymorphisms on heart diseases: Systematic review and meta-analysis of 64 case-control studies. Medicine (Baltimore). 2016;95(44):e5298.
10. Sana A, Kanwal A. The role of paraoxonase 1 (PON1) gene polymorphisms in coronary artery disease: a systematic review and meta-analysis. Biochemical Genetics. 2021;59: 919-939.
11. Kaman D, Ilhan N, Metin K, Akbulut M, Ustundag B. A preliminary study of human paraoxonase and PON1 L/M55-PON1 Q/R 192 polymorphisms in Turkish patients with coronary artery disease. Cell Biochem Funct. 2009;27(2):88-92.
12. Aynacıoğlu A, Cascorbi I, Mrozikiewicz PM, Nacak M, Tapanyiğit EE, Roots I. Paraoxonase 1 Mutations in A Turkish Population. Toxicol Appl Pharmacol.1999; 157(3):174-177.
13. Balcerzyk A, Zak I, Krauze J. Synergistic effects between Q192R polymorphism of paraoxonase 1 gene and some conventional risk factors in premature coronary artery disease. Arch Med Res. 2007;38(5):545-550.
14. Sadr-Ameli MA, Saedi S, Saedi T, Madani M, Esmaeili M, Ghardoost B. Coronary slow flow: Benign or ominous? Anatol J Cardiol. 2015;15(7), 531-535.
15. Aparicio A, Cuevas J, Morís C, Martín, M. Slow Coronary Blood Flow: Pathogenesis and Clinical Implications. Eur Cardiol. Review. 2022;17:e08.
16. Cin VG, Pekdemir H, Camsar A, et al. Diffuse intimal thickening of coronary arteries in slow coronary flow. Jpn Heart J. 2003;44(6): 907–19.
17. Catapano AL, Maggi FM, Tragni E. Low density lipoprotein oxidation, antioxidants, and atherosclerosis. Curr Opin Cardiol. 2000;15(5): 355-363.
18. Dunet V, Ruiz J, Allenbach G, Izzo P, James RW, Prior JO. Effects of paraoxonase activity and gene polymorphism on coronary vasomotion. EJNMMI Res. 2011;1(1):27.
19. International Consortium for Blood Pressure Genome-Wide Association Studies, Ehret GB, Munroe PB, et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. Nature. 2011;478(7367):103-109.
20. Kaur S, Bhatti GK, Vijayvergiya R, et al. Paraoxonase 1 Gene Polymorphisms (Q192R and L55M) Are Associated with Coronary Artery Disease Susceptibility in Asian Indians. Int J Diabetes Metab. 2018;21(1-4):38-47.
21. Ko YL, Ko YS, Wang SM, et al. The Gln-Arg 191 polymorphism of the human paraoxonase gene is not associated with the risk of coronary artery disease among Chinese in Taiwan. Atherosclerosis.1998;141(2): 259-264.

22. Sanghera DK, Saha N, Aston C, Kamboh MI. The codon 55 polymorphism in the Paraoxonase 1 gene is not associated with the risk of coronary heart disease in Asian Indians and Chinese. Atherosclerosis 1998;136(2): 217-223.
23. Abelló D, Sancho E, Camps J, Joven J. Exploring the role of paraoxonases in the pathogenesis of coronary artery disease: a systematic review. Int J Mol Sci. 2014;15(11):20997–201010.
24. Karakaya A, Ibis S, Kural T, Kose SK, Karakaya AE. Serum paraoxonase activity and phenotype distribution in Turkish subjects with coronary heart disease and its relationship to serum lipids and lipoproteins. Chem Biol Interact. 1999;118(3): 193-200.
25. Aynacioglu AS, Kepekci Y. The human paraoxonase Gln-Argl92 (Q/R) polymorphism in turkish patients with coronary artery disease. Int J Cardiol. 2000;74(1): 33-37.
26. Yildiz A, Gur M, Yilmaz R, et al. Association of paraoxonase activity and coronary blood flow. Atherosclerosis. 2008;197(1):257-263.
27. Baysal SS, Koc S. Oxidant-Antioxidant balance in patients with coronary slow flow. Pak J Med Sci. 2019;35(3):786.