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Investigation of FBXW7, MASP1 and SERP1 mRNA Expression Levels in Patients with Peripheral Artery Disease

Periferal Arter Hastalığında FBXW7, MASP1 ve SERP1 mRNA Ekspresyon Seviyelerinin İncelenmesi

[1]Bekir ERDOĞAN, [2]Sibel KURAŞ, [3]Fatih YILMAZ, [1]Fatih HACIMUSTAFAOĞLU, [4]Mahmud Esad PENÇE, [2]Halime Hanim PENÇE

[1]University Of Health Sciences, Hamidiye Vocational School of Health Services, Istanbul, Türkiye
[2]University Of Health Sciences, Hamidiye Faculty of Medicine, Department of Medical Biochemistry, Istanbul, Türkiye
[3]Antalya City Hospital, Antalya, Türkiye
[4]Uskudar University, School of Medicine, Department of Medical Biochemistry, Istanbul, Türkiye

Bekir Erdoğan: https://orcid.org/0000-0001-9637-3837
Sibel Kuraş: https://orcid.org/0000-0002-1230-7777
Fatih Yılmaz: https://orcid.org/000-0002-8439-0426
Fatih Hacımustafaoğlu: https://orcid.org/0000-0002-1429-0526
Mahmud Esad Pençe: https://orcid.org/0000-0002-8411-3138
Halime Hanim Pençe: https://orcid.org/0000-0002-8346-1018

ABSTRACT

Objective: Peripheral Artery Disease (PAD) is the third leading cause of cardiovascular morbidity worldwide. Given their established roles in lipid metabolism, the lectin-complement pathway, and endoplasmic reticulum stress, we aimed to investigate the potential involvement of the FBXW7, MASP1, and SERP1 genes in PAD. This study sought to evaluate whether these genes could serve as non-invasive biomarkers for the diagnosis of PAD, as they have not been previously explored in this patient population.

Materials and Methods: A total of 78 individuals with peripheral arterial disease and 76 healthy individuals were included in the study. Total RNA was extracted from blood samples, and the expressions of FBXW7, MASP1, and SERP1 mRNAs were determined using the real-time polymerase chain reaction (rt-PCR).

Results: No statistically significant differences were observed in the expression levels of FBXW7, MASP1, and SERP1 genes between PAD patients and healthy subjects ($p > 0.05$).

Conclusion: Although FBXW7, MASP1, and SERP1 proteins are associated with arterial function, they do not appear to play a direct role in the development of peripheral artery disease.

Keywords: FBXW7 gene, MASP1 gene, mRNA expression, Peripheral artery disease, SERP1 gene

ÖZ

Amaç: Periferik Arter Hastalığı (PAD) dünya çapında kardiyovasküler morbiditenin üçüncü önde gelen nedenidir. Daha önce çalışılmamış olan "F-Box and WD domain containing 7" (FBXW7), "mannose-binding lectin-associated serine protease 1" (MASP1) ve "stress associated endoplasmic reticulum protein 1" (SERP1) genlerinin PAD hastalığındaki potansiyel rollerini araştırmayı amaçladık.

Materyal ve Metot: Toplam 78 periferal arter hastalığı olan birey ve 76 sağlıklı birey çalışmaya dahil edilmiştir. Total RNA kan örneklerinden izole edildi ve FBXW7, MASP1 ve SERP1 mRNA ekspresyonları kantitatif gerçek zamanlı polimeraz zincir reaksiyonu kullanılarak belirlenmiştir.

Bulgular: FBXW7, MASP1 ve SERP1 genlerinin ifade düzeyleri periferik arter hastalığı olan hastalar ile sağlıklı bireyler arasında istatistiksel olarak farklılık göstermemiştir ($p>0,05$).

Sonuç: FBXW7, MASP1 ve SERP1 proteinlerinin arterle ilişkisi olmasına rağmen periferik arter hastalığının gelişiminde etkili değildirler.

Anahtar Kelimeler: FBXW7 geni, MASP1 geni, mRNA ekspresyonu, Periferik arter hastalığı, SERP1 geni

Corresponding Author / Sorumlu Yazar:
Bekir Erdoğan
Address: Selimiye, Tıbbiye Cd No: 38, 34668 Üsküdar/İstanbul, Türkiye
E-Mail: bekir.erdogan@sbu.edu.tr

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INTRODUCTION

Peripheral artery disease (PAD) is the third leading cause of cardiovascular morbidity.[1] PAD is characterized by the partial or complete obliteration of at least one peripheral artery, leading to impaired blood supply. It manifests as intermittent claudication, ischemic rest pain, and ischemic ulceration in the affected limb.[2,3] PAD pathogenesis is characterized by inflammation, endothelial dysfunction, oxidative stress, vascular remodeling, platelet activation, and thrombosis.[3] PAD patients carry a higher risk of myocardial infarction, stroke, heart failure, hypertension, and vascular death.4 Over 200 million people worldwide suffer from PAD.[2]

After the age of 60, the risk of PAD is estimated at 12-20%, increasing to 50% in those aged 85 and over. According to the National Health and Nutrition Examination Survey, the most important PAD risk factors are hypertension, diabetes, chronic kidney disease, hyperlipidemia, and smoking. Decreased high-density lipoprotein (HDL) cholesterol levels are also associated with an increased risk of death from PAD.[5,6] The combination of three or more of these risk factors increases the risk of PAD.[5] According to REACH data covering 44 countries, 46-68% of PAD patients have disease in one or more vascular beds. Likewise, 39% of patients with PAD have coronary artery disease (CAD), 10% have cerebral artery disease, and 13% have both diseases.[6,7] Lipid metabolism disruptions underlie various health problems prevalent in contemporary society, such as cardiovascular disease, obesity, and diabetes.[8]

The F-Box and WD domain containing 7 (FBXW7) protein functions as a ubiquitin-E3 targeting factor by identifying phosphorylated substrates for proteolysis. FBXW7 interacts with genes that encode sterol regulatory element-binding proteins (SREBPs) responsible for regulating cholesterol and fatty acid production. This interaction leads to the degradation of SREBPs by enhancing their ubiquitination. FBXW7 inactivation leads to the preservation of SREBP family genes, resulting in elevated levels of cholesterol synthesis, fatty acid synthesis, and LDL absorption.[9]

Mannose-binding lectin-associated serine protease 1 (MASP1) gene encodes proteins involved in the lectin complement pathway. There is a relationship between MASP serine proteases and coagulation factors. In the classical lectin pathway, MASP1 cannot produce C3 convertase alone because it cleaves C2 but not C4. However, fibrin formation is mediated by MASP2.[10,11]

Stress-associated endoplasmic reticulum protein 1 (SERP1) protein is predicted to be involved in the unfolded protein response and protein glycosylation in the endoplasmic reticulum.[12]

In light of this information, we aimed to investigate the mRNA levels of FBXW7, MASP1, and SERP1, which have not been previously studied in PAD disease, in the leukocytes of PAD patients, and to identify potential biomarker candidates.

MATERIALS AND METHODS

Ethics Committee Approval: Ethical approval for the study was obtained from the Clinical Research Ethics Committee of the Health Sciences University Hamidiye Training and Research, High Specialization Education and Research Hospital (Date: 20.12.2018, decision no: 2018/7/72). The study was conducted in accordance with the Declaration of Helsinki.

Study Groups: The study included 78 participants who presented to the cardiology outpatient clinic (Hamidiye Training and Research Hospital) between 2019 and 2020 with complaints of claudication and were assigned to the PAD group. The control group consisted of 76 age- and sex-matched patients with similar comorbidities. All patients and controls were evaluated using Doppler ultrasonography (USG) to confirm or exclude peripheral artery disease. The blood samples were collected into EDTA tubes and stored at -80°C until RNA isolation to prevent degradation. Initially, symptomatic patients underwent evaluation via Doppler USG. Subsequently, their medical therapy was optimized, and diagnostic angiography or peripheral artery interventional procedures were conducted as required. Written informed consent was obtained from all volunteers prior to their participation in the study.

Inclusion Criteria for the Patient Group:

- Patients aged 18–80 years with a confirmed diagnosis of Peripheral Artery Disease (PAD) based on clinical evaluation and imaging (Doppler USG and/or Computed Tomography Angiography).
- Presence of symptomatic PAD (intermittent claudication) classified as Rutherford Category 2–4.

Inclusion Criteria for the Control Group:

- Age- and sex-matched healthy volunteers with no clinical history of vascular disease.
- Normal vascular flow confirmed by Doppler USG to rule out asymptomatic PAD.

Exclusion Criteria (for both groups):

- Presence of any malignancy or history of chemotherapy/radiotherapy.
- Evidence of active systemic infection or chronic inflammatory diseases (e.g., Rheumatoid Arthritis, SLE).
- Severe chronic organ failure (end-stage renal disease requiring dialysis or advanced hepatic failure).
- Hematological disorders or bone marrow pathologies that could affect mRNA expression profiles.
- Critical limb ischemia (Rutherford Category 5 or 6) with tissue loss or gangrene, to avoid the confounding effects of acute necrosis.

Total RNA Isolation and Real-Time PCR: Total RNA was isolated from the blood samples using the manufacturer's protocol (Molecular Research Center Inc, Ohio, USA). The concentration and purity of the isolated total RNA samples were quantified with a spectrophotometer (Denovix DS11, USA). Samples with an A260/A280 ratio between 1.8 and 2.1 were considered pure and included in the study; those failing to meet these criteria were excluded. Complementary DNA (cDNA) was synthesized from purified RNA samples following the manufacturer's instructions (Cohesion Bioscience, UK). Subsequently, the expression levels of the synthesized cDNA samples were examined via Real-Time PCR using primers specific to each target (FBXW7, MASP1 and SERP1). GAPDH gene was used as a housekeeping gene.

The specific PCR primer sequences used in this study were as follows:

FBXW7: Forward 5'-CCACTGGGCTTGTACCATGTT-3',
Reverse 5'-GCAAAAGCCATTTCTCCCTGAA-3'

MASP1: Forward 5'-GGCAGTTCCAGCTGGATTTT-3',
Reverse 5'-CAGCTCATCCCCATACTGGT-3'

SERP1: Forward 5'-GCTGTGGTTCTTCCTGTCCT-3',
Reverse 5'-CAGGATCCAGTCCTTGACCA-3'

GAPDH: Forward 5'-GTCTCCTCTGACTTCAACAGCG-3',
Reverse 5'-ACCACCCTGTTGCTGTAGCCAA-3'

These sequences were selected based on previously validated studies and synthesized by a commercial provider.

Statistical Analysis: A post-hoc power analysis was performed to evaluate the adequacy of the sample size using G*Power software (version 3.1.9.7). Based on the sample sizes of 78 patients and 76 controls, with a type I error rate (α) of 0.05, the study had a statistical power of 86% to detect a medium effect size (Cohen's d = 0.5) in mRNA expression levels. This indicates that the sample size was sufficient to detect clinically significant differences between the groups.[3] All data were analyzed using SPSS 25.0 software. Results were analyzed within a 95% confidence interval, and statistical significance was set at $p<0.05$. For parametrically distributed data, Student's t-test was applied, while the Mann-Whitney U test was used for non-parametric distributions to compare quantitative data between groups, and Chi-square ($\chi 2$) test was used for comparing qualitative data. Post-hoc power analysis confirmed that the sample size provided 86% power to detect significant differences.

RESULTS

The study included 78 PAD patients and 76 healthy subjects. Mean age of the patient group was 58.17±8.68, while control group was 56.96±8.40 (p=0.504). The prevalence of diabetes mellitus (DM), hypertension (HT), hypercholesterolemia (HL) and coronary artery disease (CAD) did not differ significantly between the groups (p=0.510, p=0.860, p=0.458 and p=0.632; respectively). While no significant differences were observed in low-density lipoprotein (LDL)-cholesterol (p=0.601), triglyceride (p=0.514), and fasting blood glucose (p=0.645) levels, high-density lipoprotein (HDL)-cholesterol (p=0.003) and total cholesterol levels (p=0.019) were statistically significant between groups (Table 1).

Table 1. Demographic and biochemical comparison of patient and control groups.

Characterization/Parameters		Patient	Control	p
DM, n (%)	**No**	34 (45.95)	40 (54.05)	0.510[a]
	Yes	30 (51.72)	28 (48.28)	
HT, n (%)	**No**	18 (36.00)	32 (64.00)	0.860[a]
	Yes	14 (37.84)	23 (62.16)	
HL, n (%)	**No**	19 (33.93)	37 (66.07)	0.458[a]
	Yes	13 (41.94)	18 (58.06)	
CAD, n (%)	**No**	14 (77.78)	4 (22.22)	0.632[a]
	Yes	20 (71.43)	8 (28.57)	

Continuation of **Table 1**

Age, Mean±SD, (Min.-Max.)	n=63/70	58.17±8.68 (39.00-76.00)	56.96±8.40 (37.00-79.00)	0.504[b]
LDL-C, Mean±SD (Min.-Max.)	n=51/51	134.65±36.20 (52.00-254.00)	139.16±40.57 (55.00-237.00)	0.601[b]
HDL-C, Mean±SD (Min.-Max.)	n=53/52	40.11±6.82 (23.00-57.00)	45.92±9.96 (31.00-73.00)	0.003[b]
Total Cholesterol, Mean±SD (Min.-Max.)	n=20/42	187.50±43.55 (121.00-278.00)	222.12±56.52 (123.00-439.00)	0.019[b]
FBG, Mean±SD (Min.-Max.)	n=23/48	120.65±34.69 (77.00-195.00)	112.29±20.93 (81.00-181.00)	0.645[b]
Triglyceride, Mean±SD (Min.-Max.)	n=34/12	166.53±67.03 (58.00-446.00)	171.42±68.75 (51.00-254.00)	0.514[b]

[a]: Pearson Chi-square test; [b]: Mann Whitney U test; SD: standard deviation; DM: diabetes mellitus; HT: Hypertension; HL: hypercholesterolemia; CAD: coronary artery disease; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; FBG: Fasting blood glucose.

We compared FBXW7, MASP1 and SERP1 mRNA expression levels between groups according to ΔCt values, which are negatively correlated with expression levels. Some samples were excluded during statistical analysis because of unexpected melting curves. Mean of patient FBXW7 (N:71), MASP1 (N:71) and SERP1 (N:73) ΔCt values were respectively 13.45±2.74 14.21±2.65 and 10.57±1.56, while control group FBXW7 (N:67), MASP1 (N:69) and SERP1 (N:70) ΔCt value means were 13.61±2.56, 14.15±2.89, 10.84±1.08. The ΔCt values of each gene were very close between the patient and control groups. Although FBXW7 and SERP1 expressions were upregulated, while MASP1 expressions were downregulated in patient group, these changes were not statistically significant (p>0.05) (Table 2).

Table 2. Mean comparison of delta-Ct values between patient and control groups.

	Patient			**Control**			**p[a]**
	n	**ΔCt (Mean±SD)**	**ΔCt (Min-Max)**	**n**	**ΔCt (Mean±SD)**	**ΔCt (Min-Max)**	
FBXW7	71	13.45±2.74	4.82-18.14	67	13.61±2.56	7.93-16.96	0.813
MASP1	71	14.21±2.65	5.63-17.99	69	14.15±2.89	6.10-18.10	0.889
SERP1	73	10.57±1.56	3.97-15.04	70	10.84±1.08	8.13-14.71	0.433

[a]: Mann Whitney U test; SD: standard deviation; FBXW7: The F-Box and WD domain containing 7; MASP1: Mannose-binding lectin-associated serine protease 1; SERP1: Stress associated endoplasmic reticulum protein 1.

Positive correlations between FBXW7 gene and SERP1 and MASP1 genes were statistically significant (p<0.05), but MASP1-SERP1 expression correlation was not statistically significant according to Pearson correlation analysis (Table 3).

Table 3. Pearson correlation between FBXW7, MASP1 and SERP1 genes.

		n	Pearson[a]	p[b]
FBXW7	MASP1	68	0.519	**0.0000**
	SERP1	70	0.412	**0.0004**
MASP1	SERP1	70	0.129	0.2885

[a]: Pearson value. If value is higher than 0 there is positive correlation; If value lower than 0, there is negative correlation; [b]: Pearson Correlation significance value; FBXW7: The F-Box and WD domain containing 7; MASP1: Mannose-binding lectin-associated serine protease 1; SERP1: Stress associated endoplasmic reticulum protein 1.

The expression levels of FBXW7, MASP1, and SERP1 were further analyzed based on the presence of comorbidities within the study groups (Table 4). While no significant differences were observed in the expression levels of these three genes regarding the presence of DM, HL, or CAD (p>0.05), a statistically significant association was found with hypertension (HT). Specifically, the presence of HT was significantly associated with lower ΔCt values (indicating higher mRNA expression) for FBXW7 (p=0.008), MASP1 (p=0.010), and SERP1 (p=0.006) compared to non-hypertensive individuals.

Table 4. FBXW7, MASP1 and SERP1 gene expression mean comparison according to presence of comorbidities.

		FBXW7			MASP1			SERP1		
		n	**Mean±SD**	**p**	**n**	**Mean±SD**	**p**	**n**	**Mean±SD**	**p**
DM	No	34	13.41±2.56	0.733	32	14.52±2.40	0.367	34	10.68±1.47	0.825
	Yes	27	13.56±2.64		29	13.94±2.56		29	10.71±1.71	
HT	No	18	14.03±2.97	**0.008**	15	14.51±2.45	**0.010**	18	11.39±2.00	**0.006**
	Yes	14	12.27±2.04		14	12.34±2.77		13	10.91±0.57	
HL	No	19	13.34±2.82	0.659	16	12.91±3.04	0.392	18	11.12±1.93	0.873
	Yes	13	13.14±2.65		13	14.14±2.38		13	11,27±0.92	
CAD	No	12	13.91±1.86	0.785	14	15.20±1.92	0.363	14	10.31±0.88	0.753
	Yes	20	13.34±2.73		20	14.75±1.90		20	10.01±1.70	

[a]: Mann Whitney U test; SD: standard deviation; FBXW7: The F-Box and WD domain containing 7; MASP1: Mannose-binding lectin-associated serine protease 1; SERP1: Stress associated endoplasmic reticulum protein 1; DM: diabetes mellitus; HT: Hypertension; HL: hypercholesterolemia; CAD: coronary artery disease.

DISCUSSION AND CONCLUSION

Diagnosing the disease in its initial stages is crucial. The onset of PAD is usually asymptomatic, and diagnosis can be made using clinical tests such as angiography, ankle/brachial index (ABI), and pulse wave velocity. Biomarkers such as homocysteine, C-reactive protein, and fibrinogen are insufficient and inconsistent for diagnosis.[13] Previous studies have identified changes in the expression of some miRNAs in cell culture and smooth muscle cells from experimental animals compared to controls. Similarly, as in our study, there are studies examining miRNA expressions in samples from patients with PAD.[14] However, as in other diseases, the identification of non-invasive biomarkers is needed for the diagnosis of PAD and even for the evaluation of treatment. In our study, we evaluated the expression levels of FBXW7, MASP1, and SERP1 in patients with PAD. Although FBXW7 and SERP1 were upregulated and MASP1 was downregulated in the patient group, these changes did not reach statistical significance ($p>0.05$) and should be interpreted as non-significant trends. Further studies with larger cohorts are necessary to confirm if these trends represent true biological relevance in PAD progression. These results indicate that while these genes may not serve as primary diagnostic markers in their current capacity, they provide valuable molecular insights into the pathophysiology of the disease.

The pathophysiology of PAD comprises endothelial dysfunction, inflammation, thrombosis, oxidative stress, mitochondrial dysfunction, platelet activation, vascular smooth muscle cell (VSMC) activation, lipid disorders and angiogenesis. In the presence of risk factors, atherosclerotic lesions begin to form when endothelial cells and vascular smooth muscle cells are exposed to oxidized low-density lipoprotein cholesterol (ox-LDL). A fatty streak formation is followed by pathological intimal thickening, fibroatheroma, thin fibrous valvular atheroma or vulnerable plaque, plaque rupture, plaque erosion, calcified nodules, and finally fibrocalcified plaque.[15]

In addition to strategies such as smoking cessation, exercise and healthy diet, antiplatelet agents, ACE inhibitors, hypolipidemic agents, and antidiabetic agents are used to control modifiable cardiovascular risk factors in the treatment of PAD.[16] Although survival rates have increased with medical advances, there is also a need for treatments to improve the humanistic burden of disease, such as associated disabilities or quality of life. With increasing survival and aging, atherothrombotic diseases are more common and increase the economic burden.[7]

The presence of polymorphisms in the FBXW7 gene (rs2255137 and rs10033601) has been linked to the development of CAD.[17] Targeted inhibition of FBXW7 expression has been shown to improve cardiac recovery in cardiomyocyte apoptosis and myocarditis after myocardial infarction.[18] FBXW7 gene has been reported to be involved in roles such as cancer, inflammation, angiogenesis and lipogenesis regulation in previous studies.[19] Nevertheless, its contribution to cardiovascular disorders, such as peripheral artery disease (PAD), remains poorly understood. Increased lipogenesis in hepatocellular carcinoma has been shown to regulate lipogenesis by disrupting the stabilization of SREBP1 through FBXW7-mediated ubiquitylation.[20]

Recent findings indicate that MASP1 may have a promoting effect on fibrinolysis and therefore the interactions of MASP-1 with the fibrinolytic system may be important in the development and treatment of cardiovascular and thrombotic diseases.[21] In diabetic patients, which is also an important comorbidity for PAD, plasma MASP1 levels were positively correlated in prediabetic and diabetic patients.[22] MASP-1 is involved in the underlying mechanisms of vascular and ischemic diseases.

It was demonstrated by Demeter et al. that endothelial injury is exacerbated, inflammatory and pro-coagulant pathways are promoted under hypoxic conditions by MASP-1, indicating that the progression of atherothrombotic diseases such as PAD may be contributed to by dysregulation of the lectin complement pathway.[23]

Increased lectin complement pathway contributes to vascular pathology in type 1 diabetic patients. The complement system plays a role in the progression of microvascular and macrovascular complications.[24]
Additionally, blocking MASP-1 has a positive effect on the heart's performance and lessens the harm to heart tissue caused by a lack of blood flow and subsequent re-flow. This supports the idea that MASP-1 plays a key part in the process of cardiovascular diseases caused by the immune system.[25]
A study investigating the role of SERP1 in acute liver injury showed that SERP1 overexpression decreased the expression of inflammatory factors, apoptosis-associated proteins and endoplasmic reticulum stress-related proteins and reduced liver injury by regulating endoplasmic reticulum stress.[26]
In two different studies, it was shown that upregulation of two different miRNAs targeting SERP1 inhibited cell proliferation and induced apoptosis in sepsis-related lung injury. miRNAs enhance monolayer endothelial cell permeability and membrane damage by targeting SERP1, which weakens vascular barrier function involved in the development of lung injury. For this reason, both SERP1 and these two miRNAs (miR-1-3p and miR-217-5p) have been suggested to be potential biomarkers.[27,28]
The endoplasmic reticulum (ER) initiates intracellular signaling pathways known as the unfolded protein response (UPR) in response to stress. This response has been strongly linked to the development of diabetes and atherosclerosis.[29]
Researchers are studying the levels of gene expression and their probable functions to understand the underlying mechanics of PAD's development. Given the seriousness of peripheral artery disease (PAD), there is a requirement for novel and accurate biomarkers that may be utilized for diagnosis and to enhance the well-being of patients.
Although the groups were matched for age and sex, significant differences were observed in HDL-C and Total Cholesterol levels ($p<0.05$). This discrepancy likely stems from the more intensive lipid-lowering therapies (e.g., high-dose statins) typically prescribed to PAD patients compared to the control group. Furthermore, the variation in the number of subjects for certain biochemical parameters was due to missing laboratory data in some patient records, and these cases were excluded from the respective analyses.
A noteworthy finding of our study is the significant association between HT and the mRNA expression levels of *FBXW7*, *MASP1*, and *SERP1*. Patients with HT exhibited significantly higher expression levels (lower ΔCt values) for all three genes compared to those without HT ($p<0.05$). While these genes did not show a primary diagnostic value for PAD in our cohort, their upregulation in hypertensive individuals suggests a potential role in the vascular remodeling or inflammatory processes driven by high blood pressure. Specifically, the involvement of *FBXW7* in lipid metabolism and *MASP1* in the lectin-complement pathway may be modulated by the systemic stress associated with hypertension. These results indicate that comorbidities, particularly HT, are important confounding or contributing factors that should be considered in future molecular studies of vascular diseases.
A limitation of this study is the lack of longitudinal data to track expression changes over time. Future research should include functional assays and larger populations to clarify the exact mechanisms of these genes in human vascular cells and their potential as non-invasive indicators.
In conclusion, although there was no statistical significance in the differences in the expression levels of FBXW7, MASP1, and SERP1 between patients and controls, results provide valuable molecular insights into the possible roles of these genes in the pathophysiology of PAD. Large sample size of this study, relative to previous reports, strengthens the reliability of the obtained data. However, further studies are required. These should integrate functional analyses and longitudinal data. This will clarify the biological relevance of these genes. It will also clarify their potential as non-invasive indicators for PAD diagnosis and prognosis.

Ethics Committee Approval: Ethical approval for the study was obtained from the Clinical Research Ethics Committee of the Health Sciences University Hamidiye Training and Research, High Specialization Education and Research Hospital (Date: 20.12.2018, decision no: 2018/7/72). The study was conducted in accordance with the Declaration of Helsinki.
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