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Comparison of inflammatory biomarkers between peripheral artery disease patients and healthy individuals

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ABSTRACT

Objectives: This study aimed to compare inflammatory markers such as fibrinogen, C-reactive protein, and white blood cell count between patients with peripheral artery disease (PAD) and healthy individuals and investigate whether there is a relationship between low-grade inflammation and PAD.

Patients and methods: This case-control study was conducted with 162 individuals (107 males, 55 females; mean age: 52.5±13.7 years; range, 24 to 87) between January 2023 to January 2024. Eighty-seven of these participants were diagnosed with PAD by lower extremity color Doppler ultrasonography and computed tomography angiography, and the remaining 75 were healthy individuals. Biochemical results of patients and control groups were examined.

Results: Comparing the groups, statistical significance ($p<0.05$) was found according to sex, age, hypertension, diabetes mellitus, smoking, blood glucose levels, blood creatinine levels, estimated glomerular filtration rate, high-density lipoprotein, triglyceride, fibrinogen, white blood cell count, and C-reactive protein levels. In the group of PAD patients, male sex, hypertension, diabetes mellitus, and smoking were more prevalent, along with higher levels of glucose, creatinine, triglyceride, fibrinogen, white blood cell count, and C-reactive protein.

Conclusion: Inflammation biomarkers, such as fibrinogen and C-reactive protein, were found to be significantly higher in the PAD group, indicating that the low-grade inflammation hypothesis may play a role in PAD. Large-scale, prospective, randomized controlled studies on this subject are needed.

Keywords: C-reactive protein, fibrinogen, low-grade inflammation, peripheral artery disease, white blood cells.

Peripheral artery disease (PAD) occurs due to atherosclerosis, which causes stenosis or constriction in the main arteries feeding the lower extremity. Peripheral artery disease includes arterial stenosis or occlusion caused by atheromatous plaques, thrombosis, arterial inflammation, arterial dilation/aneurysm, or external pressure.[1] Development of PAD is closely associated with classical cardiovascular risk factors such as diabetes mellitus (DM), dyslipidemia, smoking, hypertension (HT), and advanced age.[1] Endothelial dysfunction is one of the earliest anomalies in the development of atherosclerosis.[2,3] Inflammation is an immune system reaction that helps defends the host by repairing damaged tissues and eliminating toxic agents. If this reaction becomes chronic and continues at a low grade, it can cause increased toxic activity of immune cells and tissue damage.[4] Low-grade inflammation is defined by increased levels of C-reactive protein (CRP) in the blood. C-reactive protein is one of the main biomarkers of inflammation in the body. The higher the level of CRP measured in the blood, the more inflammation there is in the body. Low-grade inflammation can be defined by CRP levels of 3 to 10 mg/L in the blood.[5,6] Low-grade inflammation causes changes in the homeostasis of the organism and eases the onset of chronic diseases such as DM, atherosclerosis,

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heart failure, PAD, obesity, metabolic syndrome, polycystic ovary syndrome, depression, periodontitis, osteoarthritis, and cancer.[5,6] Inflammation, besides atherosclerosis, can have a major role in the progression of PAD. The increase in inflammatory biomarkers can predict low-grade inflammation. These patients can be diagnosed and treated before disease reaches severe grades. Furthermore, preventing and treating low-grade inflammation in this group of patients can stop or slow down the progression of the disease. Yener et al.[7] found that neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio were high in patients with type D lesions according to the TASC (Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease) classification in PAD. They suggested that inflammation may play a role in the development of atherosclerosis in atherosclerotic PAD. The present study aimed to compare the levels of inflammatory biomarkers such as CRP, fibrinogen, and white blood cell (WBC) count in patients with PAD and healthy individuals.

PATIENTS AND METHODS

This case-control study was conducted with 162 individuals (107 males, 55 females; mean age: 52.5±13.7 years; range, 24 to 87) at the Ağrı Training and Research Hospital between January 2023 to January 2024. Eighty-seven of the participants were diagnosed with PAD, and the remaining 75 were healthy individuals. Biochemical results of both groups were examined. Having symptoms resembling PAD and existence of known cardiovascular risk factors were the inclusion criteria for the patient group. The exclusion criteria were age under 18 years, morbid obesity, cancer, and chronic disease such as heart failure, kidney failure, liver failure, and rheumatologic disease. These patients were not included in the study since the inflammation present in chronic diseases increases inflammatory markers. Age, sex, DM, HT, dyslipidemia, smoking, fasting blood glucose level, creatinine, estimated glomerular filtration rate (eGFR), total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, fibrinogen, and CRP levels and WBC, monocyte, lymphocyte, and platelet counts were recorded. Diabetes mellitus, HT, and dyslipidemia were diagnosed according to relevant guidelines.[8-10] A written informed consent was obtained from each patient. The study protocol was approved by the Ağrı İbrahim Çeçen University, Ethics Committee (date: 29.03.2024, no: E-98270). The study was conducted in accordance with the principles of the Declaration of Helsinki. Peripheral artery disease was diagnosed by lower extremity color Doppler ultrasonography or computed tomography angiography.

Statistical analysis

A power analysis was calculated according to creatinine levels using G*Power version 3.1.9.7 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). A power of 87% was found according to n1=75 (0.82±0.34), n_2=87 (1.16±0.83), alpha=0.05, and effect size (d)=0.49.

Data were analyzed using IBM SPSS version 27.0 (IBM Corp., Armonk, NY, USA) and MedCalc version 15.8 (MedCalc Software, Ostend, Belgium). While evaluating the data, in addition to descriptive statistical methods (frequency, percentage, mean, standard deviation, median, minimum-maximum, and interquartile range), the chi-square test was used to compare qualitative data. The suitability of the data for normal distribution was evaluated with the Kolmogorov-Smirnov test, skewness-kurtosis, and graphical methods (histograms, Q-Q plots, stem-and-leaf plots, and boxplots). In this study, for the evaluation of normally distributed quantitative data, the independent samples t-test was used. For the evaluation of data that did not show normal distribution, the Mann-Whitney U test was used. Receiver operating characteristic curves were used to determine the distinctiveness of the variables, and binary logistic regression was used to determine risk ratios. The level of statistical significance was set at $p<0.05$.

RESULTS

In comparisons made according to groups; it was found that there was a statistically significant difference ($p<0.05$) between the groups in terms of sex, age, HT, DM, smoking, fasting blood glucose, creatinine, eGFR, HDL, triglyceride, fibrinogen, and CRP levels and WBC count (Table 1).

In the PAD group, it was found that the male sex, HT, DM, and smoking rates were higher, along with older age and higher levels of fasting blood glucose, creatinine, triglyceride, fibrinogen, WBCs, and CRP (Table 2). There was no statistically significant difference between the groups in terms of other

variables (p>0.05). Variables that were considered to be more clinically significant and did not have a high correlation between the variables that showed differences in pairwise comparisons between groups (sex, age, HT, DM, smoking, glucose, creatinine, eGFR, HDL, triglyceride, fibrinogen, WBCs, monocytes, lymphocytes, platelets, and CRP) were included in the model. The backward stepwise method was used in the analysis, and the model was terminated at the ninth step. In this model, approximately 87% of the dependent variable (PAD group) could be explained (Nagelkerke R^2=0.866). According to this model, there was a statistically significant relationship between PAD status and sex, age, glucose, creatinine, fibrinogen, monocytes, platelets, and CRP (p<0.05; Table 3).

Peripheral Artery Disease (PAD) is approximately 21.52 times more prevalent in men. It is 1.07 times more common in individuals with higher age, 1.03 times more common in those with elevated glucose levels, and 0.34 times more frequent in those with increased creatinine levels. PAD is also 1.02 times more likely in individuals with higher fibrinogen levels, 1764.11 times more prevalent in those with elevated monocyte counts, 1.01 times

Table 1
Demographic characteristics of the study participants

	n	%	Mean±SD	Median	Min-Max
Age (year)			52.5±13.7	53.0	24.0-87.0
Sex					
Male	107	66.0			
Female	55	34.0			
Group					
Control group	75	46.3			
PAD group	87	53.7			
Hypertension					
Present	129	79.6			
Absent	33	20.4			
Diabetes mellitus					
Present	120	74.1			
Absent	42	25.9			
Smoking					
Present	136	83.4			
Absent	27	16.6			
Glucose (mg/dL)			123.5±61.3	97.8	66.0-348.0
Creatinine (mg/dL)			1.0±0.7	0.9	0.5-6.1
Estimated glomerular filtration rate			89.4±22.8	93.5	9.0-140.0
Cholesterol (mg/dL)			180.9±90.1	178.5	33.6-1.145.0
Low-density lipoprotein (mg/dL)			117.3±30.0	115.7	59.0-197.1
High-density lipoprotein (mg/dL)			44.8±9.7	44.0	22.5-75.9
Triglyceride (mg/dL)			171.7±155.8	132.8	46.0-1.620.4
Fibrinogen			394.1±109.2	392.0	129.3-784.0
White blood cell count (10^9\L)			7.5±2.3	7.4	0.0-14.9
Monocyte (10^9\L)			0.5±0.2	0.5	0.2-1.6
Lymphocyte (10^9\L)			2.5±1.2	2.2	0.8-8.0
Platelet (10^9\L)			302.1±130.9	267.5	140.0-869.0
C-reactive protein (mg/L)			7.2±9.7	4.8	0.2-78.0

SD: Standard deviation; PAD: Peripheral artery disease; Group K: Control group; Group H: Patient group.

Table 2
Comparisons between groups

	Control group (n=75)					PAD group (n=87)					
	n	%	Mean±SD	Median	Q1-Q3	n	%	Mean±SD	Median	Q1-Q3	*p*
Age (year)			43.81±12.63					59.99±9.53			**<0.001**b
Sex											**<0.001**a
Male	34	45.3				73	83.9				
Female	41	54.7				14	16.1				
Hypertension											**<0.001**a
Present	74	98.7				55	63.2				
Absent	1	1.3				32	36.8				
Diabetes mellitus											**<0.001**a
Present	74	98.7				46	52.9				
Absent	1	1.3				41	47.1				
Smoking											**0.020**a
Present	68	90.7				67	77.0				
Absent	7	9.3				20	23.0				
Glucose (mg/dL)			95.61±20.73					147.50±73.47			**<0.001**b
Creatinine (mg/dL)				0.79	0.65-0.92				1.02	0.79-1.18	**<0.001**c
eGFR			101.77±18.10					78.78±21.11			**<0.001**b
Cholesterol (mg/dL)				168.60	140.10-201.30				182.30	137.20-209.70	0.265c
LDL (mg/dL)			116.42±28.21					117.97±31.66			0.745b
HDL (mg/dL)			47.19±10.37					42.66±8.54			**0.003**b
Triglyceride (mg/dL)				117.20	80.00-146.00				161.60	98.70-243.40	**<0.001**c
Fibrinogen			314.57±70.71					462.58±88.09			**<0.001**b
WBC (10^9\L)			6.95±2.08					7.96±2.30			**0.004**b
Monocyte (10^9\L)			0.41±0.12					0.55±0.21			**<0.001**b
Lymphocyte (10^9\L)			2.15±0.50					2.82±1.57			**<0.001**b
Platelet (10^9\L)			266.01±51.43					333.20±166.39			**0.001**b
C-reactive protein (mg/L)				2.30	1.24-4.91				7.21	3.74-9.43	**<0.001**c

SD: Standard deviation; Q: Quartiles; eGFR: Estimated glomerular filtration rate; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; WBC: White blood cell count; Group K: Control group; Group H: Patient group; a: Chi-Square test; b: Independent Samples t test; c: Mann-Whitney U test.

Table 3
Analysis with logistic regression

	Univariate logistic regression analysis						Multivariate logistic regression analysis					
Risk factor	B	SE	Wald	OR	95% CI	*p**	B	SE	Wald	OR	95% CI	*p**
Age	0.127	0.020	40.147	1.14	1.09-1.18	<0.001	0.071	0.033	4.677	1.07	1.01-1.14	0.031
Sex	1.839	0.373	24.333	6.29	3.03-13.05	<0.001	3.069	0.973	9.958	21.52	3.20-144.79	0.002
Glucose (mg/dL)	0.029	0.007	17.162	1.03	1.02-1.04	<0.001	0.026	0.011	5.728	1.03	1.00-1.05	0.017
Creatinine (mg/dL)	2.434	0.666	13.366	11.40	3.09-42.04	<0.001	-1.073	0.452	5.627	0.34	0.14-0.83	0.018
Fibrinogen	0.024	0.003	48.135	1.02	1.02-1.03	<0.001	0.022	0.005	17.272	1.02	1.01-1.03	<0.001
Monocyte (10^9\L)	7.091	1.516	21.883	1200.97	61.56-23.431.15	<0.001	7.475	3.609	4.291	1764.11	1.50-2.080.519.22	0.038
Platelet (10^9\L)	0.005	0.002	8.773	1.01	1.00-1.01	0.003	0.010	0.005	4.288	1.01	1.00-1.02	0.038
CRP (mg/L)	0.266	0.056	22.498	1.30	1.17-1.46	<0.001	0.250	0.116	4.595	1.28	1.02-1.61	0.032
Hypertension	3.762	1.031	13.318	43.05	5.71-324.79	<0.001	--	--	--	--	--	--
DM	4.189	1.029	16.560	65.96	8.77-495.99	<0.001	--	--	--	--	--	--
Smoking	1.065	0.472	5.094	2.90	1.15-7.31	0.024	--	--	--	--	--	--
eGFR	-0.066	0.012	31.385	0.94	0.92-0.96	<0.001	--	--	--	--	--	--
HDL (mg/dL)	-0.051	0.018	8.340	0.95	0.92-0.98	0.004	--	--	--	--	--	--
Triglyceride (mg/dL)	0.005	0.002	7.747	1.01	1.00-1.01	0.005	--	--	--	--	--	--
WBC (10^9\L)	0.214	0.078	7.507	1.24	1.06-1.44	0.006	--	--	--	--	--	--
Lymphocyte (10^9\L)	0.603	0.192	9.835	1.83	1.25-2.67	0.002	--	--	--	--	--	--

SE: Standard error; OR: Odds ratio; CI: Confidence interval; CRP: C-reactive protein; DM: Diabetes mellitus; eGFR: Estimated glomerular filtration rate; HDL: High-density lipoprotein; WBC: White blood cell count; * Binary logistic regression (It is given only for the variables remaining on the model.) Nagelkerke R^2=0.866; Variable(s) removed on step 2: smoking; Step 3: WBC (10^9\L); Step 4: eGFR; Step 5: Hypertension; Step 6: HDL (mg/dL); Step 7: Lymphovyte (10^9\L); Step 8: Triglyceride (mg/dL); Step 9: DM.

Table 4
Real and predicted values according to the created model

	Predicted group		Accuracy
	Control group	PAD group	%
Real group			
Control group	71	4	94.7
PAD group	5	82	94.3
Correctly classified cases (%)			94.4

more common in those with higher platelet counts, and 1.28 times more frequent in individuals with elevated CRP levels (Table 3). A prediction table was created according to the model. Eighty-two of 87 patients (94.3%) with PAD were predicted correctly, and 71 of 75 patients (94.7%) without PAD were predicted correctly. The overall accuracy rate was found to be 94.4% (Table 4). Variables that were considered to be more clinically significant and did not have a high correlation between the variables that showed differences in pairwise comparisons between groups (fibrinogen, WBC count, and CRP) were included in the model. The backward stepwise method was used in the analysis, and the model was finalized at the second step. Approximately 67% of the dependent variable (PAD group) could be explained in this model (Nagelkerke R^2=0.665). According to this model, there was a statistically significant relationship between PAD status and fibrinogen and CRP values ($p<0.05$; Figures 1-5). Those with high fibrinogen values were approximately 1.02 times more likely to have PAD than those without, and those with high CRP values were approximately 1.18 times more likely to have PAD than those without (Table 5). A prediction table was created according to the created model. Eighty of 87 patients (92.0%) with PAD were predicted correctly, while 69 of 75 patients (92.0%) without PAD were predicted correctly. The overall accuracy rate was found to be 92.0% (Table 6).

As a result of the evaluations conducted using ROC analysis on the variables found to be different in pairwise comparisons. The cutoff points of different variables were as follows: fasting blood glucose, >110 mg/dL (area under the curve [AUC]=0.741, 95% confidence interval [CI]: 0.667-0.807, $p<0.001$); creatinine, >0.94 (AUC=0.731, 95% CI: 0.656-0.798, $p<0.001$);

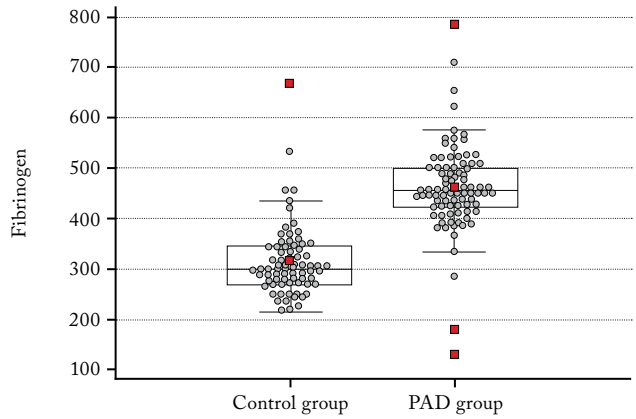

Figure 1. The range of distribution of fibrinogen values in the control and patient groups.

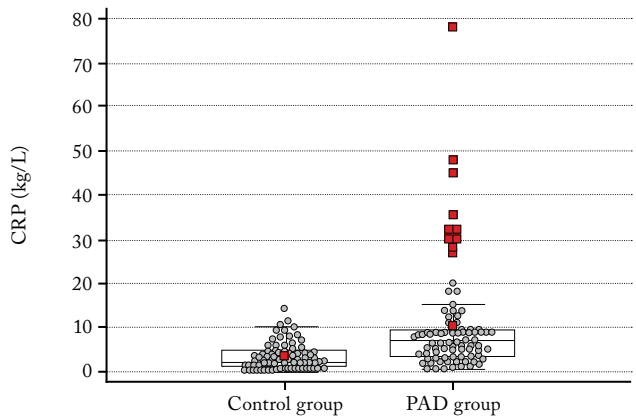

Figure 2. The range of distribution of CRP values in the study groups.

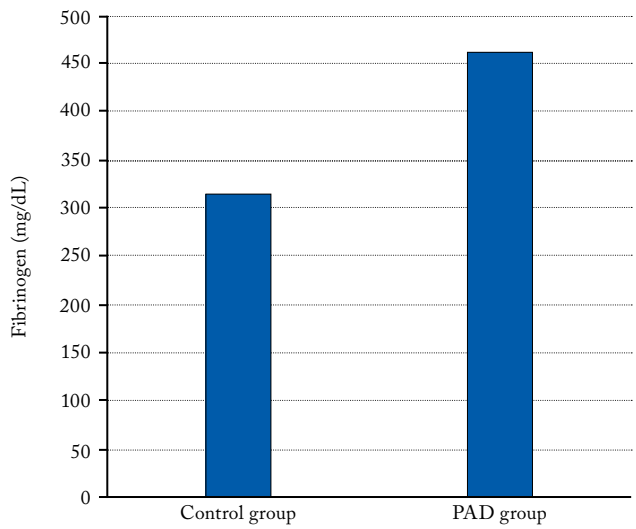

Figure 3. Fibrinogen blood levels in the patient and control groups.

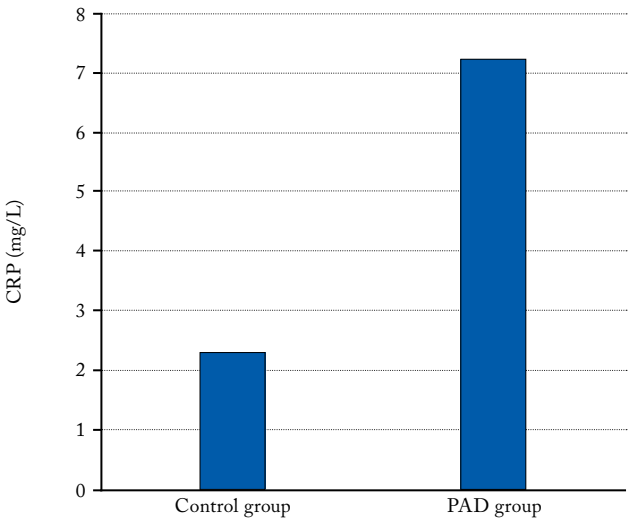

Figure 4. C-reactive protein blood levels in the patient and control groups.
CRP: C-reactive protein.

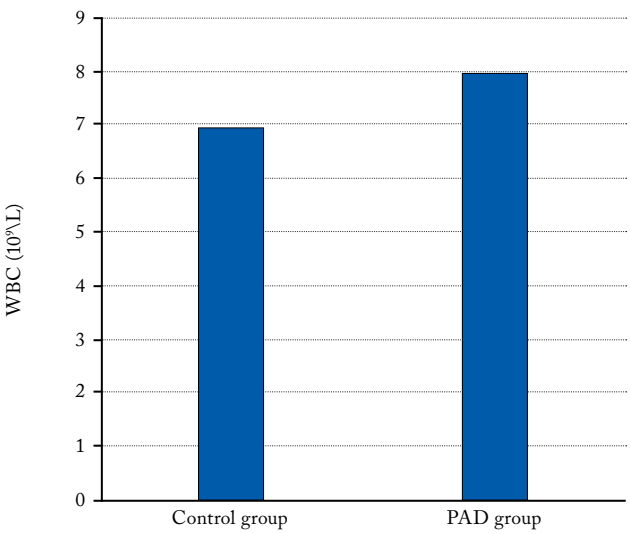

Figure 5. White blood cell count blood levels in the patient and control groups.
WBC: White blood cell count.

eGFR, ≤83 (AUC=0.803, 95% CI: 0.733-0.861, p<0.001); HDL, ≤43.8 (AUC=0.620, 95% CI: 0.540-0.695, p=0.007); triglycerides, >154.4 (AUC=0.661, 95% CI: 0.583-0.734, p<0.001); fibrinogen, >373 (AUC=0.923, 95% CI: 0.871-0.959, p<0.001); monocytes, >0.51 (AUC=0.740, 95% CI: 0.665-0.805, p<0.001); and CRP, >4.76 (AUC=0.781, 95% CI: 0.709-0.842, p<0.001) (Table 7).

Table 5
Evaluations with logistic regression

	Univariate logistic regression analysis						Multivariate logistic regression analysis					
Risk factor	B	SE	Wald	OR	95% CI	*p**	B	SE	Wald	OR	95% CI	*p**
Fibrinogen	0.024	0.003	48.135	1.02	1.02-1.03	0.000	0.021	0.003	37.758	1.02	1.01-1.03	0.000
CRP (mg/L)	0.266	0.056	22.498	1.30	1.17-1.46	0.000	0.169	0.071	5.663	1.18	1.03-1.36	0.017
WBC (10^9\L)	0.214	0.078	7.507	1.24	1.06-1.44	0.006	-	-	-	-	-	-

SE: Standard error; OR: Odds ratio; CI: Confidence interval; CRP: C-reactive protein; WBC: White blood cell count; * Binary logistic regression (It is given only for the variables remaining on the model), Nagelkerke R^2=0,665, Variable(s) removed on step 2: WBC (10^9\L).

Table 6
Real and predicted values according to the created model

	Predicted group		Accuracy
	Control group	PAD group	%
Real group			
Control group	69	6	92.0
PAD group	7	80	92.0
Correctly classified cases (%)			92.0

DISCUSSION

Our findings demonstrated a statistically significant difference in inflammation biomarkers, such as fibrinogen, CRP, and WBC count, in the PAD group compared to the control group. Proposed mechanisms by which low-grade inflammation may affect atherogenesis include increased foam cell formation via monocyte accumulation and LDL cholesterol deposition in the arterial wall.[11,12] Low-grade inflammation has been associated with an increased risk of cardiovascular events and cardiovascular mortality in various populations.[13] In a study conducted in acute myocardial infarction patients with and without DM, high-sensitivity CRP (hsCRP) was shown to predict in-hospital outcomes and two-year mortality.[14] It has also been shown that reducing low-grade inflammation in patients with coronary artery disease with or without type 2 DM reduces the residual risk of cardiovascular events.[13] In our study, the rate of DM in the PAH group was 47.1%. This finding is statistically significant (p<0.001) and is compatible with the literature (Table 2). One study reported a bidirectional relationship between DM and periodontitis, with hyperglycemic individuals having a higher prevalence of periodontitis compared to normoglycemic individuals. It has been suggested that low-grade inflammation and periodontitis increase the levels of proinflammatory mediators in the serum, which may lead to insulin resistance and diabetes.[15] It has been reported that DM and insulin resistance also trigger low-grade inflammation, and systemic inflammation is a risk factor for cardiovascular diseases, including PAD.[5,6]

One study demonstrated that HT is associated with lower-grade systemic inflammation indices in

Table 7
Receiver operating characteristic analysis

	AUC	95% CI	Cut off	Sensitivity	Specificity	Youden index	+PV	–PV	*p**
Glucose (mg/dL)	0.741	0.667-0.807	>110	55.2	85.3	0.405	81.4	62.1	**<0.001**
Creatinine (mg/dL)	0.731	0.656-0.798	>0.94	60.9	82.7	0.436	80.3	64.6	**<0.001**
eGFR	0.803	0.733-0.861	≤83	56.3	93.3	0.497	90.7	64.8	**<0.001**
HDL (mg/dL)	0.620	0.540-0.695	≤43.8	60.9	64.0	0.249	66.3	58.5	**0.007**
Triglyceride (mg/dL)	0.661	0.583-0.734	>154.4	56.3	81.3	0.377	77.8	61.6	**<0.001**
Fibrinogen	0.923	0.871-0.959	>373	94.3	89.3	0.836	91.1	93.1	**<0.001**
WBC (10^9\L)	0.641	0.562-0.714	>7.72	59.8	74.7	0.344	73.2	61.5	**0.002**
Monocyte (10^9\L)	0.740	0.665-0.805	>0.51	51.7	85.3	0.371	80.4	60.4	**<0.001**
Lymphocyte (10^9\L)	0.597	0.518-0.674	>2.74	36.8	92.0	0.288	84.2	55.6	**0.031**
Platelet (10^9\L)	0.575	0.495-0.653	>324	41.4	93.3	0.347	87.8	57.9	**0.104**
CRP (mg/L)	0.781	0.709-0.842	>4.76	72.4	74.7	0.471	76.8	70.0	**<0.001**
Monocyte/HDL ratio	0.743	0.668-0.808	>0.0106	65.5	70.7	0.362	72.2	63.9	**<0.001**
Monocytet/LDL ratio	0.673	0.595-0.744	>0.0039	63.2	64.0	0.272	67.1	60.0	**<0.001**

AUC: Under the curve; CI: Confidence interval; PV: Predictive value; * ROC curve analysis.

hypertrophic cardiomyopathy patients and that the adverse effect of HT in hypertrophic cardiomyopathy patients is a result of systemic effects rather than changes in cardiac function since left ventricular systolic and diastolic dysfunction measurements did not differ between hypertensive and normotensive patients.[16] In a review, it was stated that low-grade inflammation plays an important role in the relationship between the immune system and angiotensin II-induced HT.[17] It has been emphasized that monocyte/macrophage cells play an important role in vascular inflammation and interaction with the arterial wall throughout the progression of HT.[17] In our study, hypertension is statistically absent in 36% of patients with PAD ($p<0.001$; Table 2). One of the risk factors for PAH is dyslipidemia.[1] The risk of early atherosclerotic cardiovascular disease dramatically increases in patients with lipid disorders.[8] Recent studies have shown a definite link between systemic low-grade inflammation and obesity and dyslipidemia, with both disorders being associated with endothelial dysfunction/activation, a proinflammatory and prothrombotic state of the endothelium leading to the infiltration of leukocytes into the arterial wall.[18-20] In our study, the average triglyceride value in the PAD group was 161.60 mg/dL (98.70-243.40 mg/dL), with statistical significance ($p<0.001$; Table 2). Smoking, one of the other risk factors of PAD, is one of the most important preventable factors causing this disease.[1] Cigarette smoke extracts activate the NLRP3 inflammasome via reactive oxygen species, resulting in the downstream release of interleukin (IL)-1 beta, IL-18, and other inflammatory factors, leading to functional changes such as autophagy, pyrolysis, and apoptosis in endothelial cells.[19-21] According to our findings, the rate of smokers in the PAD group was 23% and this results was compatible with the literature (Table 2). In their study investigating the effect of physical activity on inflammation in PAD patients, Christofaro et al.[22] found that high hsCRP values were associated with inflammation and that hsCRP values significantly decreased in patients who engaged in regular physical activity. Jacobs et al.,[23] in their study on patients with metabolic syndrome, investigated CRP, IL-6, sVCAM-1 (soluble vascular cell adhesion molecule-1), sICAM-1 (soluble intercellular adhesion molecule-1), and serum amyloid A levels. They found a partial association between metabolic syndrome and the prevalence of coronary artery disease and PAD severity, suggesting that this relationship was mediated by low-grade inflammation. In our study, the mean fibrinogen 462.58±88.09 mg/dL and mean CRP 7.21±9.7 (3.74-9.43) mg/L values were high and were statistically significant ($p<0.001$). We observed other noteworthy findings in this study. For example, the mean monocyte and lymphocyte values were higher in the PAD group (0.55±0.21 and 2.82±1.57, respectively), with statistical significance ($p<0.001$). Barhoumi et al.[17] demonstrated that monocyte activation plays a role in vascular inflammation and low-grade inflammation.

This study had several limitations, including a small sample size and a retrospective design. Additionally, it would have been more valuable if other inflammatory biomarkers, such as tumor necrosis factor-alpha and IL-6, had been analyzed in this study.

In conclusion, inflammatory biomarkers such as fibrinogen, CRP, and WBC count were found to be statistically significant in the PAD group, indicating that the low-grade inflammation hypothesis may play a role in PAD. If the role of low-grade inflammation in PAD is proven in future large-scale, prospective, randomized controlled trials, anti-inflammatory treatment modalities may be incorporated into PAD treatment.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Wang W, Zhao T, Geng K, Yuan G, Chen Y, Xu Y. Smoking and the pathophysiology of peripheral artery disease. Front Cardiovasc Med 2021;8:704106. doi: 10.3389/fcvm.2021.704106.
2. Gimbrone MA Jr, García-Cardeña G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. Circ Res 2016;118:620-36. doi: 10.1161/CIRCRESAHA.115.306301.
3. Donato AJ, Morgan RG, Walker AE, Lesniewski LA. Cellular and molecular biology of aging endothelial cells. J Mol Cell Cardiol 2015;89:122-35. doi: 10.1016/j.yjmcc.2015.01.021.

4. Alur İ. Low-grade inflammation: A familiar factor in cardiovascular diseases. JACC Basic Transl Sci 2023;8:1475. doi: 10.1016/j.jacbts.2023.09.010.
5. Tristan Asensi M, Napoletano A, Sofi F, Dinu M. Low-grade inflammation and ultra-processed foods consumption: A review. Nutrients 2023;15:1546. doi: 10.3390/nu15061546.
6. Cecoro G, Annunziata M, Iuorio MT, Nastri L, Guida L. Periodontitis, low-grade inflammation and systemic health: A scoping review. Medicina (Kaunas) 2020;56:272. doi: 10.3390/medicina56060272.
7. Yener AU, Cicek OF, Cicek MC, Ozkan T, Korkmaz K, Yener O, et al. Does a basic blood test tell the location of peripheral arterial lesions? Acta Medica Mediterranea 2015;31:377.
8. Handelsman Y, Bloomgarden ZT, Grunberger G, Umpierrez G, Zimmerman RS, Bailey TS, et al. American Association of Clinical Endocrinologists and American College of Endocrinology--Clinical practice guidelines for developing a diabetes mellitus comprehensive care plan--2015. Endocr Pract 2015;21:413-37.
9. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: The task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2013;34:2159-219. doi: 10.1093/eurheartj/eht151.
10. National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-421.
11. Torzewski M, Rist C, Mortensen RF, Zwaka TP, Bienek M, Waltenberger J, et al. C-reactive protein in the arterial intima: Role of C-reactive protein receptor-dependent monocyte recruitment in atherogenesis. Arterioscler Thromb Vasc Biol 2000;20:2094-9. doi: 10.1161/01.atv.20.9.2094.
12. Zwaka TP, Hombach V, Torzewski J. C-reactive protein-mediated low density lipoprotein uptake by macrophages: implications for atherosclerosis. Circulation 2001;103:1194-7. doi: 10.1161/01.cir.103.9.1194.
13. Sharif S, Van der Graaf Y, Cramer MJ, Kapelle LJ, de Borst GJ, Visseren FLJ, et al. Low-grade inflammation as a risk factor for cardiovascular events and all-cause mortality in patients with type 2 diabetes. Cardiovasc Diabetol 2021;20:220. doi: 10.1186/s12933-021-01409-0.
14. Lucci C, Cosentino N, Genovese S, Campodonico J, Milazzo V, De Metrio M, et al. Prognostic impact of admission high-sensitivity C-reactive protein in acute myocardial infarction patients with and without diabetes mellitus. Cardiovasc Diabetol 2020;19:183. doi: 10.1186/s12933-020-01157-7.
15. Sima C, Glogauer M. Diabetes mellitus and periodontal diseases. Curr Diab Rep 2013;13:445-52. doi: 10.1007/s11892-013-0367-y.
16. Zach DK, Schwegel N, Santner V, Winkelbauer L, Hoeller V, Kolesnik E, et al. Low-grade systemic inflammation and left ventricular dysfunction in hypertensive compared to non-hypertensive hypertrophic cardiomyopathy. Int J Cardiol 2024;399:131661. doi: 10.1016/j.ijcard.2023.131661.
17. Barhoumi T, Todryk S. Role of monocytes/macrophages in renin-angiotensin system-induced hypertension and end organ damage. Front Physiol 2023;14:1199934. doi: 10.3389/fphys.2023.1199934.
18. Domingo E, Marques P, Francisco V, Piqueras L, Sanz MJ. Targeting systemic inflammation in metabolic disorders. A therapeutic candidate for the prevention of cardiovascular diseases? Pharmacol Res 2024;200:107058. doi: 10.1016/j.phrs.2024.107058.
19. Ismaeel A, Brumberg RS, Kirk JS, Papoutsi E, Farmer PJ, Bohannon WT, et al. Oxidative stress and arterial dysfunction in peripheral artery disease. Antioxidants (Basel) 2018;7:145. doi: 10.3390/antiox7100145.
20. Wu X, Zhang H, Qi W, Zhang Y, Li J, Li Z, et al. Nicotine promotes atherosclerosis via ROS-NLRP3-mediated endothelial cell pyroptosis. Cell Death Dis 2018;9:171. doi: 10.1038/s41419-017-0257-3.
21. Wang X, Bian Y, Zhang R, Liu X, Ni L, Ma B, et al. Melatonin alleviates cigarette smoke-induced endothelial cell pyroptosis through inhibiting ROS/NLRP3 axis. Biochem Biophys Res Commun 2019;519:402-8. doi: 10.1016/j.bbrc.2019.09.005.
22. Christofaro DGD, Ritti-Dias RM, Tebar WR, Werneck AO, Bittencourt MS, Cucato GG, et al. Are C-reactive protein concentrations affected by smoking status and physical activity levels? A longitudinal study. PLoS One 2023;18:e0293453. doi: 10.1371/journal.pone.0293453.
23. Jacobs M, van Greevenbroek MM, van der Kallen CJ, Ferreira I, Blaak EE, Feskens EJ, et al. Low-grade inflammation can partly explain the association between the metabolic syndrome and either coronary artery disease or severity of peripheral arterial disease: The CODAM study. Eur J Clin Invest 2009;39:437-44. doi: 10.1111/j.1365-2362.2009.02129.x.