



ANGIOTENSIN-CONVERTING ENZYME GENE INSERTION/DELETION POLYMORPHISM IN PERIPHERAL ARTERIAL OCCLUSIVE DISEASE

Aneliya Avramova^{1*}, Emil Slavov¹, Resmi Ismail², Todor Valkov², Dimitar Petkov^{2, 3}, Lyuba Miteva¹

1)Department of Molecular Biology, Immunology and Medical Genetics, Faculty of Medicine, Trakia University, Stara Zagora, Bulgaria.

2)University Hospital for Active Treatment "Trakia", Stara Zagora, Bulgaria.

3)Department "Special Surgery", Faculty of Medicine, Trakia University, Stara Zagora, Bulgaria.

ABSTRACT:

Purpose: Peripheral Arterial Occlusive Disease (PAOD) is a vascular disease associated with high morbidity and mortality worldwide. The angiotensin-converting enzyme (ACE) insertion/deletion (I/D) gene polymorphism (rs4340) has been suggested as a potential risk factor for PAOD. This study aimed to examine the association of the ACE I/D polymorphism and PAOD risk in Bulgarian patients.

Materials/Methods: This case-control study included 85 patients with PAOD and 394 controls. Genomic DNA was isolated from peripheral blood, and ACE genotyping was performed using classical end-point polymerase chain reaction.

Results: ACE genotype frequencies were similar between PAOD patients (DD: 0.317; ID: 0.459; II:0.224) and controls (DD: 0.345; ID: 0.495; II: 0.160; $p=0.368$), as well as the allelic frequencies ($p=0.274$). Further analysis based on the clinical manifestation of the disease did not reveal a significant association with the ACE I/D polymorphism. However, a tendency for a higher frequency of the DD-genotype was observed among cases with arterial hypertension (0.348 vs. 0.188) or with atrophic changes (0.412 vs. 0.294), compared to patients without these conditions.

Conclusion: There was no significant association between the ACE I/D polymorphism and the development of PAOD in the Bulgarian population. However, carrying the DD-genotype might contribute to the clinical characteristics of PAOD.

Key words: Peripheral Arterial Occlusive Disease, ACE I/D polymorphism, rs4340, hypertension,

INTRODUCTION

Peripheral Arterial Occlusive Disease (PAOD) is a specific form of Peripheral Arterial Disease (PAD), an atherosclerotic disease associated with increasing global morbidity and mortality [1]. Between 1990 and 2019, the global prevalence of PAD rose by 72.5 % with PAD-related mortality doubling over the same period. The actual burden of PAOD is probably greater than the statistical data in world health, as data on the prevalence of asymptomatic PAD are incomplete. Even in asymptomatic PAD, the risk of premature death is similar to that of symptomatic PAD and significantly higher than that of those without PAD [2]. A prospective study showed that within one year, 21% of asymptomatic PAD patients developed claudication symptoms, indicating the potential for rapid disease progression [3].

Patients with PAD are at higher risk for cardiovascular complications, including stroke, transient ischemic attack and heart attack [4]. While atherosclerosis remains the well-established pathological basis of PAD, emerging evidence highlights the role of the coagulation system, especially during the early stages of plaque development [5].

Inflammatory cells within the early lesion contribute to the expression of procoagulant factors, which are more prominent in early rather than advanced atherosclerotic plaques [6]. Thrombus formation over disrupted plaque is a key event in the onset of the acute cardiovascular events [7]. The coagulation regulation is crucial for the development of the disease. The Renin-Angiotensin-Aldosterone System (RAAS) is a major regulator of vascular homeostasis. Its dysregulation is implicated in hypertension, myocardial infarction, stroke, and cardio-renal syndromes [8]. Angiotensin converting enzyme (ACE) plays a central role in RAAS. ACE converts angiotensin I (Ang I) to angiotensin II (Ang II), degrades bradykinin and indirectly decreases fibrinolysis [9].

The human ACE gene contains an insertion/deletion (I/D) polymorphism of an *Alu* element in intron 16, which has been associated with variability of human serum ACE levels. A recent systematic review by Kumari N et al. (2022)

summarized that the D-allele of the ACE I/D polymorphism is significantly associated with an increased risk of cardiovascular disease (CVD) [10]. The authors also highlighted substantial inter-ethnic differences in genotype and allele frequencies. However, the role of the ACE I/D polymorphism as a genetic marker for PAOD remains controversial. A significantly higher prevalence of the D-allele was reported among 281 Italian PAD patients compared to clinically healthy volunteers [11]. In contrast, another case-control study involving 522 PAD patients and 522 matched controls from Austria found no significant association between PAD risk and ACE I/D polymorphism [12]. To the best of our knowledge, no studies have investigated the relationship between the ACE I/D polymorphism and PAOD in the Bulgarian population.

In light of the above, the aim of the present case-control study was to investigate the potential role of the ACE gene I/D polymorphism as a predisposing factor for PAOD, or as a factor involved in modulating the severity of the disease.

MATERIALS AND METHODS:

Subjects

The case-control study included 85 patients with PAOD (61 men and 24 women) and 394 controls. The patients were admitted to the Department of Vascular Surgery, Hospital for Active Treatment “Trakia”, Stara Zagora, Bulgaria. The study was approved by the Ethics Committee of the Medical Faculty, Trakia University, Bulgaria (approval number: 30/25.04.2024). Informed consent was obtained from all participants in accordance with the ethical standards of the Helsinki Declaration.

The diagnosis of PAOD was based on the clinical diagnostic criteria, Doppler sonography, ankle-brachial index (ABI), angiography. The mean age of the PAOD group was 65.56 ± 10.93 years, with no significant differences between men and women (64.7 ± 11.61 years vs. 67.8 ± 8.83 years, $p=0.250$).

Symptoms such as paresthesias, cold extremities, fatigue and/or claudication had been present for more than 6 months among 82.35% of patients. The stage of the disease was assessed using the Fontaine classification. Asymptomatic or intermittent claudication was observed in 22 patients (25.9%), rest pain in 43 patients (50.6%), and ischemic ulcers or gangrene in 20 patients (23.5%).

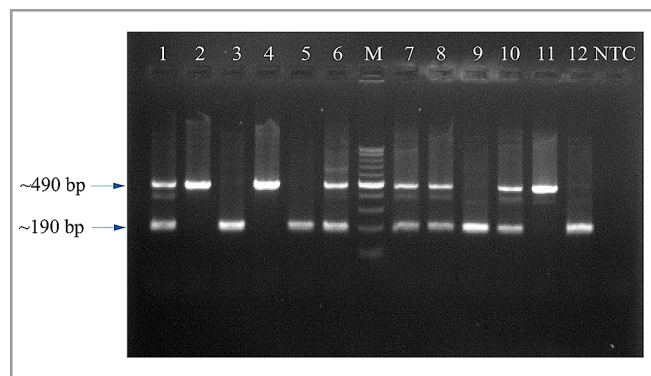
Clinical evaluation included assessment of claudication, hypoesthesia, trophic changes, wound lesions in the affected limb. The patient group was further analyzed based on anatomical localization of PAOD, and associated risk factors, including arterial hypertension, diabetes mellitus, tobacco smoking, stroke, ischemic heart disease, and dyslipidemia.

Genotyping of the ACE I/D polymorphism

Genomic DNA was isolated from peripheral blood samples, and ACE genotyping was performed using classical end-point polymerase chain reaction (PCR). The PCR mixture contained the following components: forward primer 5'-CTGGAGACCACTCCCATCCTTTCT-3', reverse primer 5'-GATGTGGCCATCACATTCGTCAGAT-3', 3mM

MgCl₂, 0.2 mM dNTPs, Taq DNA polymerase, 10x PCR buffer and 20-50 ng of template DNA. PCR amplification was carried out in a GeneAmp PCR System 9700 (Applied Biosystems, Foster City, CA, USA) under the following cycling condition: 10 min initial denaturation at 94°C followed by 30 cycles of 94 °C for 1 min, 58 °C for 1 min, and 72 °C for 1 min, followed by a final extension at 72°C for 7 min. The PCR products were visualized by 2% agarose gel electrophoresis. The presence of a 490bp fragment indicated the insertion (I) allele, and a 190bp fragment indicated the deletion (D) allele (Fig. 1).

Fig. 1. Visualization of PCR products by 2.0 % agarose gel electrophoresis.



Genomic DNA was extracted from peripheral blood samples and amplified by PCR using primers flanking the insertion/deletion (I/D) polymorphic region in intron 16 of the ACE gene. PCR products were separated on a 2% agarose gel and visualized with ethidium bromide staining under UV light.

A band at 490 bp corresponds to the insertion (I) allele, while a band at 90 bp corresponds to the deletion (D) allele. NTC – non-template control; Lane M: DNA ladder (100 bp marker); Lanes 1, 6, 7, 8 and 10: Heterozygous (I/D) genotype – two bands at 490 bp and 190 bp; Lanes 2, 4 and 11: Homozygous insertion (I/I) genotype – single band at 490 bp; Lanes 3, 5, 9 and 12: Homozygous deletion (D/D) genotype – single band at 190 bp.

Statistical analysis

The results were analyzed using STATISTICA v.12 software (StatSoft, OK, USA). The chi-square test was used for categorical variables, including genotype, gender, clinical characteristics, hypertension, diabetes, tobacco smoking, stroke, ischemic heart disease, and dyslipidemia. Fisher's exact test was applied if one or more cells had a count less than 5.

Different inheritance models – allelic model (D-allele vs. I-allele), dominant (ID+DD vs. II), and recessive (DD vs. ID+II), were used to assess the potential association between the ACE I/D polymorphism and PAOD risk. Logistic regression was conducted to estimate odds ratio (ORs) and 95% confidence intervals (CIs). The differences were considered statistically significant at p -value < 0.05 .

RESULTS:

The genotypes and allele frequencies of the ACE I/D polymorphism among the controls and cases are summarized in Table 1. No significant association between ACE

I/D polymorphism and PAOD risk in our Bulgarian patients was established under the dominant, recessive model, and the allelic model.

Table 1. Allele and genotypes frequencies of the ACE I/D polymorphism in PAOD patients and controls.

Frequency	Casesn (%)	Controlsn (%)	OR (95%CI)	p value
Genotype				
DD	27 (31.76)	136 (34.52)	ref	
ID	39 (45.88)	195 (49.49)	1.007 (0.589-1.724)	0.979
II	19 (22.35)	63 (15.99)	1.519 (0.786-2.935)	0.211
Dominant model				
DD & ID	66 (77.65)	331 (84.01)	ref	
II	19 (22.35)	63 (15.99)	1.513 (0.849-2.693)	0.158
Recessive model				
DD	27 (31.76)	136 (34.52)	ref	
ID & II	58 (68.24)	258 (65.48)	1.132 (0.686-1.870)	0.627
Allelic model				
D	93 (54.71)	467 (59.26)	ref	
I	77 (45.29)	321 (40.74)	1.205 (0.863-1.682)	0.274

No significant differences were observed between PAOD cases according to sex and age of onset. Although the prevalence of early-onset PAOD (diagnosed age d" 50) in the studied group is low, it should be noted that all PAOD (n=6) were carrier of the D-allele. Respectively, the D-allele frequency was higher among cases with early-onset than among cases diagnosed at 51 years or older (0.67 vs. 0.53), although this difference did not reach statistical significance.

Next, subgroup analysis was performed based on the clinical manifestations (Table 2) and associated conditions (Table 3) of PAOD.

Table 2. Genotype distribution of the ACE I/D polymorphism in PAOD patients according to the clinical manifestations.

Clinical manifestations			
Genotype/allele	Yesn (%)	Non (%)	p-value
Fontaine classification - IV stage			
DD	8 (40.00)	19 (29.23)	
ID	7 (35.00)	32 (49.23)	0.266
II	5 (25.00)	14 (21.54)	0.806
D-allele	23 (57.50)	70 (53.85)	
I-allele	17 (42.50)	60 (46.15)	0.685
Multiple arterial occlusions			
DD	17 (36.95)	10 (25.64)	
ID	17 (36.95)	22 (56.41)	0.122
II	12 (26.09)	7 (17.95)	0.989

D-allele	51 (55.43)	42 (53.85)	
I-allele	41 (44.57)	36 (46.15)	0.836
Claudication			
DD	24 (32.00)	3 (30.00)	
ID	34 (45.33)	5 (50.00)	0.834
II	17 (26.67)	2 (20.00)	0.950
D-allele	82 (54.67)	11 (55.00)	
I-allele	68 (45.33)	9 (45.00)	0.978
Atrophic changes			
DD	7 (41.18)	20 (29.41)	
ID	5 (29.41)	34 (50.00)	0.175
II	5 (29.41)	14 (20.59)	0.976
D-allele	19 (55.88)	74 (54.44)	
I-allele	15 (44.12)	62 (45.56)	0.878

The femoral arteries were the most frequently affected (n=54, 63.5%), and among 46 patients (54.1%) multiple arterial occlusions were observed. There was a trend toward a higher frequency of the DD-genotype among patients with ischemic ulcers or gangrene (0.400 vs. 0.292, OR=1.614; 95% CI: 0.569-4.576; p=0.366), popliteal occlusion (0.421 vs 0.234; OR=2.38; 95 % CI: 0.936-6.051; p=0.066); with multiple arterial occlusions (0.37 vs. 0.256, OR=1.700; 95% CI: 0.667-4.332; p=0.264), and patients with atrophic changes (0.412 vs. 0.294; OR=1.68; 95 % CI:0.560-5.036; p=0.351). Although these associations did not reach statistical significance, the observed trends may suggest a possible role of the DD genotype in more severe or complex PAOD presentations.

Table 3. Genotype distribution of the ACE I/D polymorphism in PAOD patients according to the associated conditions.

Associated conditions			
Genotype	Yes n (%)	No n (%)	p-value
Arterial hypertension			
DD	24 (34.78)	3 (18.75)	
ID	31 (44.93)	8 (50.00)	0.502
II	14 (20.29)	5 (31.25)	0.345
D-allele	79 (57.25)	14 (43.75)	
I-allele	59 (42.75)	18 (56.25)	0.167
Diabetes			
DD	8 (22.22)	19 (38.78)	
ID	19 (52.78)	20 (40.82)	0.121
II	9 (25.00)	10 (20.41)	0.220
D-allele	35 (48.61)	58 (59.18)	
I-allele	37 (51.39)	40 (40.82)	0.171
Stroke			
DD	0 (0.00)	27 (34.18)	
ID	5 (83.33)	34 (43.04)	0.144
II	1 (16.67)	18 (22.78)	0.858
D-allele	5 (41.67)	88 (55.70)	
I-allele	7 (58.33)	70 (44.30)	0.347
Ischemic heart disease			
DD	2 (16.67)	25 (34.25)	
ID	4 (33.33)	35 (47.95)	1.00
II	6 (50.00)	13 (17.81)	0.083
D-allele	8 (33.33)	85 (58.22)	
I-allele	16 (66.67)	61 (41.78)	0.023
Dyslipidemia			
DD	5 (20.83)	22 (36.07)	
ID	11 (45.83)	28 (45.90)	0.367
II	8 (33.33)	11 (18.03)	0.080
D-allele	21 (43.75)	72 (59.02)	
I-allele	27 (56.25)	50 (40.98)	0.072

Arterial hypertension (81.18%) as well as diabetes (34.1%) were the most common comorbidities in PAOD patients. No statistically significant differences in genotype distribution were found with respect to co-existence of arterial hypertension, diabetes, stroke and dyslipidemia (Table 3). A tendency for a higher frequency of the DD-genotype was observed among cases with arterial hypertension (0.348 vs. 0.188) compared to normotensive patients. Among patients with ischemic heart disease, the frequency of the D-allele was significantly lower (0.333 vs. 0.582; OR

= 0.359; 95 % CI: 0.144-0.892; p=0.023). However, these results should be interpreted with caution due to the small sample sizes in some subgroups, particularly where contingency tables included cells with fewer than five observations. The genotype and allele frequencies did not differ significantly between smoking and non-smoking PAOD patients.

DISCUSSION:

The present study investigates the association between the ACE I/D polymorphism and PAOD, as well as its relationship with clinical and demographic factors among Bulgarian patients.

While the genetic contribution to complex diseases like PAOD remains a topic of active investigations, growing evidence supports the notion that gene-environment interactions significantly influence disease risk [13]. Complex diseases are often the result of multiple genetic and environmental factors. In this regard, many modifiable risk factor such as smoking, dyslipidemia, arterial hypertension, obesity, and diabetes play a pivotal role in the development and progression of PAOD.

The ACE I/D polymorphism has been associated with variability in human serum ACE levels. Previous studies suggest a dose-dependent effect of the D allele on ACE serum levels [14]. Elevated ACE levels may contribute to vascular remodeling, endothelial dysfunction, and altered fibrinolysis via upregulation of the RAAS system. However, our data did not demonstrate a significant association between the ACE I/D polymorphism and PAOD risk. The similarity in allelic and genotype frequencies between cases and controls suggests no direct role of this polymorphism in POAD pathogenesis. This finding aligns with a meta-analysis of 13 studies, which reported no significant overall association between ACE I/D polymorphism and PAD risk and suggested possible ethnic differences in genetic background and living environment [15]. Similar results of lack of association between PAD and ACE I/D polymorphism have been reported in other studies [16, 17]. In contrast, a regional analysis by [11] reported an increased frequency of the D-allele as a risk factor for PAD with a 2.1-fold higher risk for individuals with the homozygous DD genotype. Although further large-scale studies in different ethnic groups are needed, our data suggest that the ACE I/D polymorphism may not directly contribute to PAOD susceptibility, but it might influence clinical disease characteristics.

In our study, we observed a 1.4-fold higher frequency of the DD genotype among patients with atrophic changes. Given the pivotal role of ACE in the production of the vasoconstrictor - Ang II [18], it is plausible that higher ACE levels encoded by the DD-genotype may contribute to microvessels vasoconstriction, leading to insufficient tissue perfusion and subsequent tissue ischemia [19]. Furthermore, there was a trend toward higher DD-genotype frequency among patients with IV stage PAOD (Fontaine classification) and in those with multiple arterial occlusions. Notably, it should be noted that all patients diagnosed with PAOD before age 50 were carrier of the D-allele.

lele. Respectively, the D-allele frequency was higher among early-onset cases than in those diagnosed after age 50 years (0.67 vs. 0.53), although this difference did not reach statistical significance. A previous study involving 522 PAD patients reported significant earlier disease onset in men (58.2 years) compared to women (65.8 years) [12]. Our findings support the possibility of earlier disease onset among men, though the difference was not statistically significant.

The present study did not reveal a significant association between the ACE I/D polymorphism and smoking or comorbidities such as dyslipidemia, diabetes, and stroke. Interestingly, the frequency of the DD genotype was significantly lower among patients with ischemic heart disease; however, this finding should be interpreted with caution due to the limited number of patients presenting with both ischemic heart disease and concomitant PAOD. Furthermore, ischemic heart disease and PAOD may act as independent risk factors for one another, reflecting their shared atherosclerotic pathophysiology. In addition, we observed a trend toward a higher DD genotype frequency among patients with arterial hypertension. A similar study by Karagiannisa A, et al. 2004 in a close geographic region - northern Greece, involving a comparable sample size, also reported no significant associations between the ACE I/D genotype and the studied comorbidities [16]. In contrast, Tseng C, et al. 2011 reported that the traditional risk factors, hypertension, smoking and dyslipidemia, play an important role in the association between ACE genotypes and PAD among patients from Taiwan [20]. The authors suggested that patients with the DD genotype and traditional risk factors are at the highest risk.

This study has some limitations that should be considered when interpreting the results. First, the relatively

small sample size of the PAOD group, particularly in subgroup analyses which may affect the robustness of the findings. Second, as the study population was limited to Bulgarian patients, the results may not be generalizable to other ethnic or regional populations.

CONCLUSION:

Our findings do not support a significant association between the ACE I/D polymorphism and overall PAOD risk in the Bulgarian population. However, the carrying of the DD genotype might influence the clinical presentation of PAOD, earlier disease onset, greater severity, and a potential association with hypertension. Further large-scale studies in diverse populations are warranted to better understand the potential role of this genetic variant in the pathogenesis and clinical course of PAOD.

Abbreviations:

ABI - ankle-brachial index
ACE - Angiotensin-converting enzyme
Ang - Angiotensin
CI - confidence interval
CVD - Cardiovascular disease
I/D - insertion/deletion
OR - odds ratio
PAD - Peripheral Arterial Disease
PAOD - Peripheral Arterial Occlusive Disease
PCR - Polymerase chain reaction
RAAS - Renin-Angiotensin-Aldosterone System

Acknowledgements:

This work was supported by the Medical Faculty, Trakia University, under Grant no. NIP11/2024

REFERENCES:

1. Deng L, Du C, Liu L, Wang Y, Gu H, Armstrong DG, et al. Forecasting the Global Burden of Peripheral Artery Disease from 2021 to 2050: A Population-Based Study. *Research (Wash D C)*. 2025 Jul 1;8:0702. [[PubMed](#)]
2. Diehm C, Allenberg JR, Pittrow D, Mahn M, Tepohl G, Haberl RL, et al. Mortality and vascular morbidity in older adults with asymptomatic versus symptomatic peripheral artery disease. *Circulation*. 2009 Nov 24;120(21):2053-61. [[PubMed](#)]
3. Behroozian AA, Beckman JA. Asymptomatic peripheral artery disease: Silent but deadly. *Prog Cardiovasc Dis*. 2021 Mar-Apr;65:2-8. [[PubMed](#)]
4. Martin SS, Aday AW, Allen NB, Almarzooq ZI, Anderson CAM, Arora P, et al. 2025 Heart Disease and Stroke Statistics: A Report of US and Global Data From the American Heart Association. *Circulation*. 2025 Jan 27;151(8):e41-e660. [[Crossref](#)]
5. Mandaglio-Collados D, Marín F, Rivera-Caravaca JM. Peripheral artery disease: Update on etiology, pathophysiology, diagnosis and treatment. *Med Clin (Barc)*. 2023 Oct 27;161(8):344-350. [[PubMed](#)]
6. Miceli G, Basso MG, Rizzo G, Pintus C, Tuttolomondo A. The Role of the Coagulation System in Peripheral Arterial Disease: Interactions with the Arterial Wall and Its Vascular Microenvironment and Implications for Rational Therapies. *Int J Mol Sci*. 2022 Nov 29;23(23):14914. [[PubMed](#)]
7. Asada Y, Yamashita A, Sato Y, Hatakeyama K. Pathophysiology of atherothrombosis: Mechanisms of thrombus formation on disrupted atherosclerotic plaques. *Pathol Int*. 2020 Jun;70(6):309-322. [[PubMed](#)]
8. Sobhy M, Eletriby A, Ragy H, Kandil H, Saleh MA, Farag N, et al. ACE Inhibitors and Angiotensin Receptor Blockers for the Primary and Secondary Prevention of Cardiovascular Outcomes: Recommendations from the 2024 Egyptian Cardiology Expert Consensus in Collaboration with the CVREP Foundation. *Cardiol Ther*. 2024 Dec;13(4):707-736. [[PubMed](#)]
9. Thakur S, Sharma V, Kaur D, Purkait P. Angiotensin-Converting Enzyme (ACE) Insertion/Deletion (I/D) Polymorphism as a Conjoint Regulator of Coagulation, Fibrinolytic, and RAAS Pathway in Infertility and Associated Pregnancy Complications. *J Renin Angiotensin Aldosterone Syst*. 2022 Nov 29;2022:1695769. [[PubMed](#)]
10. Kumari N, Yadav A, Ahirwar R,

Sagar SK, Mondal PR. Angiotensin converting enzyme (ACE) insertion / deletion (I/D) polymorphism and its association with cardiovascular adversities – A systematic review. *Human Gene*. 2022 Oct 1;34:201117. [[Crossref](#)]

11. Fatini C, Sticchi E, Sofi F, Said AA, Pratesi G, Pulli R, et al. Multilocus analysis in candidate genes ACE, AGT, and AGTR1 and predisposition to peripheral arterial disease: role of ACE D/-240T haplotype. *J Vasc Surg*. 2009 Dec;50(6):1399-404. [[PubMed](#)]

12. Renner W, Pabst E, Paulweber B, Malaimare L, Iglseder B, Wascher TC, et al. The angiotensin-converting-enzyme insertion/deletion polymorphism is not a risk factor for peripheral arterial disease. *Atherosclerosis*. 2002 Nov;165(1):175-8. [[PubMed](#)]

13. Gagneur J, Stegle O, Zhu C, Jakob P, Tekkedil MM, Aiyar RS, et al.

Genotype-Environment Interactions Reveal Causal Pathways That Mediate Genetic Effects on Phenotype. *PLoS Genet*. 2013; 9(9):e1003803. [[PubMed](#)]

14. Wong MKS. Subchapter 42D - Angiotensin converting enzyme. *Handbook of Hormones (Second edition)*. 2021 Aug;1:505-508. [[Crossref](#)]

15. Han C, Han XK, Liu FC, Huang JF. Ethnic differences in the association between angiotensin-converting enzyme gene insertion/deletion polymorphism and peripheral vascular disease: A meta-analysis. *Chronic Dis Transl Med*. 2017 Sep 18;3(4):230-241. [[PubMed](#)]

16. Karagiannisa A, Balaska K, Tziomalosa K, Gerasimidis T, Karamanos D, Papayeyriou A, et al. Lack of an association between angiotensin converting enzyme gene polymorphism and peripheral arterial occlusive disease. *Vasc Med*. 2004

May;9(3):189-92. [[PubMed](#)]

17. Yalým Z, Onrat ST, Yalým SA, Aldemir M, Av°ar A, Dođan I, et al. The effects of genetic polymorphisms and diabetes mellitus on the development of peripheral artery disease. *Turk Kardiyol Dern Ars*. 2020 Jul;48(5):484-49. [[PubMed](#)]

18. Le D, Brown L, Malik K, Murakami S. Two Opposing Functions of Angiotensin-Converting Enzyme (ACE) That Links Hypertension, Dementia, and Aging. *Int J Mol Sci*. 2021 Dec 7;22(24):13178. [[PubMed](#)]

19. Chade AR. Renal Vascular Structure and Rarefaction. *Compr Physiol*. 2013 Apr;3(2):817-31. [[PubMed](#)]

20. Tseng CH, Tseng FH, Chong CK, Tseng CP, Cheng JC. Angiotensin-converting enzyme genotype and peripheral arterial disease in diabetic patients. *Exp Diabetes Res*. 2012;2012:698695. [[PubMed](#)]

Please cite this article as: Avramova A, Slavov E, Ismail R, Valkov T, Petkov D, Miteva L. Angiotensin-converting enzyme gene insertion/deletion polymorphism in peripheral arterial occlusive disease. *J of IMAB*. 2026 Jan-Mar;32(1):6726-6731. [[Crossref](#) - <https://doi.org/10.5272/jimab.2026321.6726>]

Received: 30/07/2025; Published online: 20/02/2026



Address for correspondence:

Aneliya Avramova,
Department of Molecular Biology, Immunology and Medical Genetics, Faculty of Medicine, Trakia University, Stara Zagora,
11, Armeyska Str., 6000 Stara Zagora, Bulgaria,
E-mail: ani85avramova@yahoo.com,