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M U N D A R I J A

THE ROLE OF APOLIPOPROTEIN E IN ATHEROSCLEROTIC RENAL ARTERY DISEASE

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Annotation. Cardiovascular diseases remain the leading cause of morbidity and mortality worldwide, with atherosclerosis being a major underlying pathology. Among the various manifestations of atherosclerosis, atherosclerotic renal artery disease (ARAD) is of particular clinical importance due to its association with renovascular hypertension, chronic kidney disease (CKD), and an increased risk of cardiovascular events. Despite advancements in diagnostic and therapeutic approaches, ARAD often progresses silently and is frequently diagnosed at advanced stages, making early identification of risk factors crucial.

Keywords: chronic kidney disease, renal artery atherosclerosis, APOE, gene, polymorphism.

BUYRAK ARTERIAYALARI ATEROSKLEROZIDA ANGIOTENSINOGEN (AGT) GENINING RO‘LI

Nazarova Nigina Otabek qizi
PhD, Katta o‘qituvchi, Toshkent Davlat Tibbiyot Universiteti

Annotatsiya. Yurak-qon tomir kasalliklari butun dunyo bo‘ylab kasallanish va o‘limning yetakchi sabablaridan biri bo‘lib qolmoqda, bunda ateroskleroz asosiy patologiya hisoblanadi. Aterosklerozning turli ko‘rinishlari orasida buyrak arteriyalarining aterosklerotik zararlanishi (BAAZ) alohida klinik ahamiyatga ega, chunki u renovaskulyar gipertenziya, surunkali buyrak kasalligi (SBK) va yurak-qon tomir asoratlari xavfining ortishi bilan bog‘liq. Diagnostika va davolash usullarining rivojlanishiga qaramay, BAAZ ko‘pincha hech qanday belgisiz kechadi va ko‘pincha kech bosqichlarda aniqlanadi, bu esa xavf omillarini erta aniqlashni juda muhim qiladi.

Kalit so‘zlar: surunkali buyrak kasalligi, buyrak arteriyalarining aterosklerozi, APOE, gen, polimorfizm.

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Introduction

In recent years, attention has increasingly turned to the genetic and molecular mechanisms underlying atherosclerosis, with particular focus on lipid metabolism and its regulation. One of the key molecules in this context is Apolipoprotein E (ApoE) — a polymorphic protein involved in the transport and clearance of lipoproteins in plasma [7; B-23].

ApoE plays a central role in maintaining lipid homeostasis by mediating the interaction of lipoprotein particles with specific receptors in the liver and peripheral tissues. There are three common isoforms of ApoE (E2, E3, and E4), encoded by different alleles (ε2, ε3, ε4), and these isoforms exhibit distinct functional properties [1; B-7].

Notably, the ApoE ε4 allele has been associated with increased plasma cholesterol levels, impaired lipid clearance, and enhanced inflammatory responses — all of which

contribute to accelerated atherogenesis. Several studies suggest a correlation between ApoE polymorphisms and susceptibility to atherosclerotic lesions in various vascular beds, including the renal arteries[6; B-11].

Given these findings, exploring the role of Apolipoprotein E in ARAD is of great relevance. It holds promise not only for improving our understanding of disease mechanisms but also for identifying genetic markers for early risk assessment and personalized therapeutic strategies. The topic aligns with current trends in precision medicine and highlights the importance of integrating molecular genetics into clinical nephrology and cardiology[2; B-23].

The following literature review explores the current understanding of the relationship between Apolipoprotein E (ApoE) and atherosclerotic renal artery disease (ARAD), focusing on the genetic, molecular, and clinical implications of ApoE polymorphisms in the pathogenesis and progression of this condition[5; B-22].

Atherosclerotic renal artery disease (ARAD) is a progressive condition characterized by the narrowing of the renal arteries due to the buildup of atherosclerotic plaques. It is a leading cause of secondary hypertension and chronic kidney disease, particularly in elderly individuals with widespread systemic atherosclerosis (Safian & Textor, 2001). The pathophysiology of ARAD is complex and multifactorial, involving dyslipidemia, endothelial dysfunction, inflammation, and genetic predispositions[3; B-3].

Apolipoprotein E (ApoE) is a 34-kDa protein involved in lipid metabolism and plays a vital role in the transport and clearance of cholesterol-rich lipoproteins (Mahley & Rall, 2000). ApoE is encoded by the APOE gene , which exists in three common allelic forms: ε2, ε3, and ε4 . These isoforms differ in their receptor-binding affinities and impact on lipid profiles. The ε3 allele is the most common and considered neutral, while the ε4 allele has been consistently linked to increased total cholesterol, LDL-C levels, and greater cardiovascular risk, including accelerated atherosclerosis (Eichner et al., 2002) [8,9 ; B-7].

In the context of renal artery disease, several studies have investigated the role of ApoE polymorphisms. For example, a study by Kamei et al. (2003) found that individuals carrying the ApoE ε4 allele had a higher prevalence of renal artery stenosis compared to those with ε3/ε3 genotypes. Similarly, research by Arinami et al. (1997) demonstrated a correlation between ApoE ε4 and generalized atherosclerotic lesions, including renal vasculature involvement[4; B-9].

Moreover, ApoE has been implicated in modulating inflammatory responses and oxidative stress, both of which contribute to endothelial injury and plaque instability (Zhou et al., 2006). Animal models of ApoE-deficiency (ApoE−/− mice) develop spontaneous atherosclerotic lesions, including in renal arteries, supporting its central role in disease development (Zhang et al., 1992).

On a molecular level, ApoE interacts with LDL receptors and heparan sulfate proteoglycans, influencing lipid uptake in vascular smooth muscle and macrophages. The altered lipid handling in ApoE ε4 carriers may exacerbate foam cell formation, a hallmark of atherogenesis (Mahley et al., 2009).

Despite these findings, there is still a limited number of studies focusing specifically on ApoE's role in atherosclerotic renal artery disease compared to its extensively studied effects in coronary and cerebral arteries. Further research is needed to establish clear clinical

correlations and to evaluate whether ApoE genotyping could serve as a biomarker for early detection or risk stratification in patients at risk for ARAD.

Would you like the references formatted in APA, MLA, or another style? Or shall we continue with the next section (e.g., objectives, methodology, etc.)?

Materials and methods.

The object of the research work in 2024-2025, the object of the study was 30 patients with Chronic kidney disease in chronic heart failure who were treated in inpatient departments of cardiology and therapy of the multidisciplinary clinic of the Tashkent Medical Academy. Also, 32 healthy individual were selected for the control group.

The subject of the study. As the subject of the study, the results of genotype and alleles of the Leu28Pro polymorphism APOE genes in the blood plasma of patients with CKD were obtained.

The study used genetic (APOE gene) to determine polymorphisms of Leu28Pro used electrophoretic detection and statistical methods.

62 people took part in the study, of which 30 people made up the main group and 32 people were external to the control group. In turn, the main group was divided into 2 groups according to the type of case-control.Group 1 is a group of patients with CHF who did not develop CKD (n=15), of which men n=5 (33,3%), women n=10 (66,7%), the average age was 46.4±1.9 years**.** Group 2 is a group of patients with CHF, with developed CKD (n=15). There were n=5 (33,3%), n=64 women n=10 (66,7%), the average age was 46.7±2 years.

For the control group, DNA samples of healthy donors were taken from the DNA bank for laboratory and instrumental studies, blood of healthy individuals for genetic studies.

Before the start of the study, patients who applied to the hospital were selected, and all patients included in the study were examined on the 2nd day of inpatient treatment and on the 1st day of outpatient treatment. The studies were conducted from January 2024 to May 2025. Before the start of the study, the functional state of the kidneys in each patient was assessed by glomerular filtration rate (GFR) and creatinine concentration using the 2011 modification of the 2009 formula, and all the results were documented.

DNA isolation and analysis of polymorphic gene markers were carried out at the Center for Scientific and Practical Medicine of Hematology of the Ministry of Health of the Republic of Uzbekistan. In the process of molecular genetic research, electrophoretic detection methods were used to isolate DNA from peripheral blood lymphocytes. To control the population, DNA samples (n=32) of conditionally healthy donors (without CKD markers) were provided from the DNA bank of the Department of Molecular Medicine and Cellular Technologies of this center.

The Leu28Pro marker of the APOE gene. The Leu28Pro marker of the APOE gene consists of 3 genotypes Leu/Leu, Leu/Pro, Pro/Pro. A comparative analysis of the prevalence of alleles and genotypes in patients of the main and control groups was carried out.

The prevalence of the Leu allele in the studied main and control groups was 89.7% and 94.9%, respectively. The prevalence of the functionally unfavorable Pro allele was 10.3% and 5.1% in a comparable population. According to the results of the statistical report, compared with carriers of the Pro allele, carriers of the Leuallele are 2.1 times more likely to develop the disease, and it was found that the difference between them has significant statistical significance (x2=4.2; P=0.05; OR=2.1; 95% CI 1.03–4.4). The Thr allele showed a protective

effect against the development of the disease (x2=4.2; P=0.05; OR=0.5; 95% CI 0.23-0.97) (see Table 1).

According to the results obtained in the main and control groups, the prevalence of Leu/Leu, Leu/Pro, Pro/Pro genotypes was 82.1%, 15.4%, 2.6% and 90.7%, 8.3% and 0.9%. According to statistical analysis, carriers of the Pro/Pro genotype were 2.8 times more likely to develop the disease than carriers of the Leu/Pro genotype (x2=0.9; P=0.4; OR=2.8; 95% CI 0.32-25.01). The Pro/Pro genotype prevailed in the control group compared to the main group, was 90.7% and 82.1%, respectively, and showed a probability of predisposition to the development of the disease (x2=3.6; P=0.1; OR =0.5; 95% CI 0,21–1,03). The Leu/Pro genotype was also more common in the main group compared to the control group and was 15.4 and 8.3%, respectively, and the probability of developing the disease was high (x2=2.6; P=0.2; OR=2.0; 95% CI 0.87–4.61).

Table- 1

The prevalence of alleles and genotypes of the polymorphic marker Leu28Pro of the APOE gene in patients of the main and control groups.

Alleles and genotypes	The number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	The main group		The control group							
	n	%	n	%						
Leu	210	89,7	205	94,9	4,2	p = 0,05	0,9	0,59 - 1,52	0,5	0,23 - 0,97
Pro	24	10,3	11	5,1	4,2	p = 0,05	1,1	0,4 - 2,81	2,1	1,03 - 4,4
Leu/ Leu	96	82,1	98	90,7	3,6	p = 0,1	0,9	0,52 - 1,57	0,5	0,21 - 1,03
Leu / Pro	18	15,4	9	8,3	2,6	p = 0,2	1,8	1,02 - 3,33	2,0	0,87 - 4,61
Pro / Pro	3	2,6	1	0,9	0,9	p = 0,4	2,8	0,89 - 8,63	2,8	0,32 - 25,01

In the studied groups 1 and 2, the prevalence of the Leu allele was 92.6% and 87.9%, respectively. The prevalence of the functionally unfavorable Pro allele was 7.4% and 12.1% in the corresponding population. According to the results of the statistical report, compared with carriers of the Leu allele, carriers of the Pro allele had a 1.7-fold higher probability of developing the disease (x2=1.3; P=0.3; OR=1.7; 95% CI 0.69-4.28). The Leu allele (x2=1.3; P=0.3; OR=0.6; 95% CI 0.23-1.45) showed a protective effect against the development of the disease (see Table 2).

Table-2

The prevalence of alleles and genotypes of the polymorphic marker Leu28Pro of the APOE gene in the 1st and 2nd observation groups

Alleles and genotypes	The number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	With CKD		Without CKD							
	n	%	n	%						
Leu	123	87,9	87	92,6	1,3	p = 0,3	0,9	0,55 - 1,65	0,6	0,23 - 1,45
Pro	17	12,1	7	7,4	1,3	p = 0,3	1,1	0,3 - 3,72	1,7	0,69 - 4,28
Leu/ Leu	56	80,0	40	85,1	0,5	p = 0,5	0,9	0,48 - 1,85	0,7	0,26 - 1,89
Leu / Pro	11	15,7	7	14,9	0,0	p = 0,95	1,1	0,48 - 2,32	1,1	0,38 - 2,98

According to the results obtained in groups 1 and 2, the prevalence of Leu/Leu, Leu/Pro, Pro/Pro genotypes was 80.0%, 15.7%, 0% and 85.1%, 14.9% 0%, respectively. According to statistical analysis, carriers of the Leu/Pro genotype were 1.1 times more likely to develop the disease than carriers of the Leu/Leu genotype, and the difference between them was not statistically significant (x2=0; P=0.95; OR=1.1; 95% CI 0.38–2.98). The Leu/Leu genotype prevailed in group 1 compared to group 2, amounting to 85.1 and 80.0%, respectively, and showed a protective effect on the development of the disease (x2=0.5; P=0.5; OR=0, 7; 95% CI 0,26–1,89). The Leu/Pro genotype was more common in group 2 compared to group 1 and was 14.9 and 15.7%, respectively, and the probability of developing the disease was low (x2=0; P=0.95; OR=1.1; 95% CI 0.38–2.98).

It should be noted that according to the results of genetic testing of alleles and genotypes of the polymorphic marker Leu/Pro of the APOE gene, when comparing the main and control groups, the functionally unfavorable Pro allele in the main group (x2=4.2; P =0.05; OR=2.1; 95% CI 1.03-4.4) and Leu/Leu genotypes (x2=0.9; P=0.4; OR=2.8; 95% CI 0.32-25.01) have a high tendency to develop the disease, and reliable statistical significance has been established between them. The Leu allele (x2=4.2; P=0.05; OR=0.5; 95% CI 0.23-0.97) showed a protective effect against the development of the disease.

Discussion.

When analyzing these statistical results, it was found that the early or late development of the disease in some patients is associated with the interaction of not only one gene, but also another gene. At the same time, early development of the disease is observed due to the combined action of a functionally unfavorable genotype and alleles of two genes, and vice versa, the development of the disease may be observed later due to the protective properties of genotypes and alleles of two genes, however, a functionally unfavorable genotype and alleles of one gene may occur.

Based on the above information and the results of all examinations, we recommend introducing genetic testing into standard methods of examination of patients of Uzbek nationality. After all, this method allows you to determine the development of CKD before its

clinical manifestation. This will help doctors diagnose patients, select appropriate treatment and lengthen the period before hemodialysis by early detection of the development of lupus nephritis. In addition, the risk of early disability caused by the disease will decrease.

Conclusion.

The incidence of functionally unfavorable The Pro allele of the LEU28Pro polymorphic marker of the AGT gene was 10.3%, OR=2.1 (95%CI 1.03-4.4), the frequency of occurrence of the mutant heterozygous Leu/Pro genotype was 15.4%, OR=2.0 (95% CI 0.87-4.61), and the frequency of occurrence of the mutant homozygous genotype Pro/Pro was 2.6%, OO=2.8 (95% CI 0.32-25.01).

Адабиётлар/Литература/References

1. Sezer S, Tutal E, Arat Z, et al. Arterial atherosclerosis in patients with chronic kidney disease and its relationship with serum and tissue endothelin-1. *J Ren Nutr.* (corrected). PMID: 19841523. ([PubMed][5])
2. Dhaun N, Webb DJ, Kluth DC. Endothelin-1 and the kidney – beyond BP. *Br J Pharmacol.* 2012;167(4):720–731. ([NCBI][4])
3. Cho ME, Brunt VE, Shiu YT, et al. Endothelial dysfunction in chronic kidney disease: a clinical perspective. *Am J Physiol Heart Circ Physiol.* (PMC). ([PMC][2])
4. Endothelin-A receptor antagonism modifies cardiovascular risk factors in CKD. *PubMed.* PMID: 23243212. ([PubMed][7])
5. Namuun G, Kadota A, Hisamatsu T, et al. Relationship between Kidney Function and Subclinical Atherosclerosis Progression Evaluated by Coronary Artery Calcification. *J Atheroscler Thromb.* 2021;29(9):1359–1371. ([PMC][8])
6. Назарова, Н. О., & Жаббаров, О. О. (2025). РИСК АТЕРОСКЛЕРОЗА У ПАЦИЕНТОВ С ХРОНИЧЕСКОЙ БОЛЕЗНЬЮ ПОЧЕК.
7. Khaydarov, R., Umarova, Z. F., & Nazarova, N. O. (2025). RENAL HEMODYNAMIC CHANGES IN LUPUS NEPHRITIS. Медицинский журнал молодых ученых, (13 (03)), 216-220.
8. Nazarova, N. O., & Jabbarov, O. O. (2025). APOL1 NEPHROPATHY RISK VARIANTS AND INCIDENT CARDIOVASCULAR DISEASE EVENTS. Медицинский журнал молодых ученых, (13 (03)), 60-63.
9. Salimov, J. K., Umarova, Z. F., & Nazarova, N. O. (2025). THE USE OF ENOXAPARIN AND RIVAROXABAN IN PATIENTS WITH CHRONIC KIDNEY DISEASE. Инновационные исследования в современном мире: теория и практика, 4(3), 105-106.

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