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Association Of The Lys198asn Polymorphism Of The Edn1 Gene With Its Expression Level And The Risk Of Essential Arterial Hypertension In Patients With Obesity

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ABSTRACT

Obesity is a significant prognostic factor in the development of arterial hypertension; however, the molecular-genetic mechanisms underlying this association have not been fully studied. It provides a detailed examination of key genetic polymorphisms associated with both obesity and hypertension. Particular attention is given to the role of endothelial dysfunction as one of the central pathological mechanisms contributing to the progression of hypertension in obese patients. Additionally, the study explores the potential implementation of genetic biomarkers for risk stratification and the development of personalized therapeutic approaches aimed at preventing and treating arterial hypertension in this patient group.

Keywords: *Essential hypertension, obesity, genetic polymorphism, EDN1, endothelin-1*

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1. INTRODUCTION

Epidemiological data published in JAMA (2020) indicate a persistently high prevalence of essential arterial hypertension (EAH) in the U.S. population, despite significant advancements in antihypertensive pharmacotherapy [11]. A scientific statement from the American Heart Association (AHA), presented by Powell-Wiley et al. (2021), emphasizes obesity as an independent predictor of cardiovascular diseases (CVD), including EAH, highlighting the need for in-depth exploration of pathophysiological mechanisms associated with adiposity and the development of innovative strategies for its management and prevention [12].

In recent years, research has increasingly focused on endothelial dysfunction (ED) as a pivotal component in the pathogenesis of EAH. Studies by Ambrosino P. et al. (2022) and Drożdż D. et al. (2023) demonstrate that the foundation of CVD and ED lies in disrupted endothelial homeostasis, driven by suppressed expression of endothelial nitric oxide synthase (eNOS) and excessive production of endothelin-1 (ET-1). These alterations not only precede the onset of EAH but also exacerbate its progression, establishing a self-sustaining cycle of pathological processes [8, 10].

Contemporary molecular-genetic studies underscore the critical role of genetic determinants in the diagnosis and risk stratification of CVD [5]. Extensive evidence confirms the association of single nucleotide polymorphisms (SNPs) with the development of cardiovascular pathology, enabling their use as biomarkers of predisposition [1, 6]. Particular attention

is given to candidate genes involved in blood pressure regulation, with the endothelin-1 gene (EDN1) standing out prominently. Polymorphisms in EDN1 may modulate plasma ET-1 levels, contributing to hypertensive states [3, 4]. However, the specific impact of these SNPs on EAH pathogenesis warrants further investigation [2].

Thus, advances in genomics have identified a broad spectrum of polymorphisms that are crucial for regulating endothelial function and vascular tone. In this context, the EDN1 gene is of particular interest, as its allelic variants are associated with alterations in blood pressure regulation mechanisms. Comprehensive analysis of these genetic markers enhances the precision of individual CVD risk assessment and paves the way for personalized prevention and treatment strategies based on patients' genetic profiles.

Purpose of the study: To investigate the association of the Lys198Asn polymorphism of the EDN1 gene with its expression level and the risk of developing essential arterial hypertension in patients with obesity.

Material and methods of research. The study included 276 individuals, with 171 patients forming the main cohort, stratified into three comparative subgroups. The first subgroup (n=57) comprised individuals with EAH without obesity; the second subgroup (n=59) included patients with comorbid EAH and obesity; and the third subgroup (n=55) consisted of individuals with obesity but no history or clinical manifestations of arterial hypertension (AH) at the time of examination. The control group included 105 conditionally healthy individuals without signs of EAH or obesity, both at the time of examination and in their medical history.

All study cohorts underwent a structured, multi-stage clinical and instrumental assessment aimed at comprehensively evaluating the patients' somatic status and identifying key predictors of EAH development. The initial stage involved a detailed medical history collection, including an assessment of familial cardiovascular disease predisposition, identification of known risk factors, and analysis of behavioral habits potentially affecting cardiovascular health, such as dietary patterns, physical activity levels, exposure to chronic stress, and harmful habits (e.g., smoking, alcohol consumption). The subsequent stage included a clinical-physical examination, during which arterial blood pressure (BP), heart rate (HR), and basic anthropometric measurements (height, body weight, waist circumference) were recorded, followed by the calculation of body mass index (BMI) to stratify obesity-related risk.

Genetic testing played a central role in the study, focusing on identifying functionally significant polymorphisms associated with the pathogenesis of AH and vascular dysfunction, specifically the Lys198Asn polymorphism of the EDN1 gene. Genotyping was conducted at the Department of Molecular Medicine and Cellular Technologies (headed by Professor Kh.Ya. Karimov) and the Laboratory of Medical Genetics (headed by Professor K.T. Boboev) at the Republican Specialized Scientific-Practical Medical Center of Hematology, Ministry of Health of the Republic of Uzbekistan. The genetic component of the study involved several sequential steps: collection of peripheral venous blood samples from patients and controls; isolation of genomic DNA from blood plasma lymphocytes; polymerase chain reaction (PCR), including both standard and real-time PCR (RT-PCR); and, when necessary, electrophoresis with subsequent visualization of amplification results.

Additionally, enzyme-linked immunosorbent assay (ELISA) was performed to measure serum levels of the vascular biomarker endothelin-1 (ET-1), enabling an assessment of endothelial function and its potential role in the pathogenesis of EAH in the study participants.

To standardize and systematize the collected data, a system of individual electronic medical records was implemented. These records included all relevant information: medical history, physical examination findings, laboratory, and instrumental data, ensuring comprehensive clinical-diagnostic support throughout all stages of the study.

The results obtained and their discussion. Between 2024 and 2025, a comprehensive clinical and laboratory examination was conducted on 171 patients admitted for inpatient treatment in the cardiology departments of the Andijan State Medical Institute (ASMI) clinic and the Andijan Branch of the Republican Specialized Scientific-Practical Medical Center of Cardiology (AB RSPMCC). Additionally, the study included patients seeking medical care at the polyclinic of the Andijan Branch of the Republican Specialized Scientific-Practical Medical Center of Endocrinology (AB RSPMCE). All study participants were matched by sex and age to ensure the validity of statistical analysis; however, differences were observed between groups in clinically significant parameters, such as body mass index (BMI), blood pressure levels, and disease duration. The mean age of the main study group was as follows: Group I (patients with EAH without obesity): 61.8 ± 1.46 years, with men (n=28) averaging 60.6 ± 2.27 years and women (n=29) 63.0 ± 1.60 years; Group II (patients with EAH and obesity): 61.8 ± 1.98 years, with men (n=22) averaging 62.5 ± 2.12 years and women (n=37) 61.4 ± 3.56 years; Group III (patients with obesity but no diagnosed AH): 44.5 ± 0.00 years, with men (n=12) averaging 37.1 ± 0.00 years and women (n=43) 46.6 ± 0.00 years. The control group consisted of 105 conditionally healthy individuals with no history or clinical manifestations of AH or obesity.

Comparative analysis of genotype distribution revealed that the Lys/Lys genotype was the most prevalent, occurring in 64.9% of cases (111 genotypes examined) in the main group and 70.5% of cases (74 genotypes examined) in the control group. No statistically significant differences were observed ($\chi^2 = 0.9$, $p = 0.40$), with an odds ratio (OR) of 0.8 (95% CI: 0.46–1.31). The heterozygous Lys/Asn genotype was identified in 28.7% of cases (49 genotypes examined) in the main group and 26.7% of cases (28 genotypes examined) in the control group, showing no significant differences ($\chi^2 = 0.1$, $p = 0.80$) and an OR of 1.1 (95% CI: 0.64–1.9). The Asn/Asn genotype was the least common, observed in 6.4% of cases (11 genotypes examined) in the main group and 2.9% of cases (3 genotypes examined) in the control group. Although no statistically significant differences were found ($\chi^2 = 1.7$, $p = 0.20$), the odds ratio (OR = 2.3, 95% CI: 0.66–8.29) suggests a trend toward a higher frequency of this genotype in the main group. This may indicate a potential association between the Asn/Asn genotype and constitutional court is required for confirmation of this hypothesis.

In continuation of the above, an in-depth comparative analysis was conducted between the study groups, enabling a detailed characterization of the distribution patterns of genotypic variants of the Lys198Asn polymorphism of the EDN1 gene (Table 1). The analysis of genotypes revealed that the homozygous Lys/Lys variant was identified in 63.2% of patients in group I and 54.2% of patients in group II. The chi-square test yielded a value of $\chi^2 = 1.0$, $p = 0.40$, indicating no significant difference between the groups. The odds ratio (OR) of 1.4 (95% CI: 0.69–3.04) suggests a slight increase in the likelihood of this genotype in patients without obesity; however, the confidence interval crossing unity renders this result statistically non-significant. The heterozygous Lys/Asn variant exhibited nearly identical frequencies in both groups (33.3% vs. 33.9%). Statistical analysis ($\chi^2 = 0.0$, $p = 0.95$) demonstrated no association of this genotype with the presence of obesity. The odds ratio of OR = 1.0 (95% CI: 0.45–2.11) further confirms the absence of a statistically significant relationship. The homozygous Asn/Asn variant was observed in 3.5% of patients in group I and 11.9% of patients in group II. The statistical parameters ($\chi^2 = 2.8$, $p = 0.10$) indicate a trend toward a higher frequency of this genotype among patients with EAH and obesity, although the significance level does not meet the threshold for statistical reliability. The calculated odds ratio of OR = 0.3 (95% CI: 0.06–1.24) suggests a potential association of this genotype with obesity; however, the small sample size and wide confidence interval necessitate further investigation to elucidate this relationship.

Table 1. Comparative analysis of genotype frequencies of the Lys198Asn polymorphism of the EDN1 gene between patient groups with EAH and obesity (n = 276)

Lys198Asn genotypes	**number of examined genotypes**				**χ2**	**p**	**OR**	**95%CI**
group I (patients with EAH without obesity) group II (patients with EAH and obesity)								
	n	**%**	**n**	**%**				
Lys/Lys	36	63,2	32	54,2	1,0	0,40	1,4	0,69 - 3,04
Lys/Asn	19	33,3	20	33,9	0,0	0,95	1,0	0,45 - 2,11
Asn/Asn	2	3,5	7	11,9	2,8	0,10	0,3	0,06 - 1,24
group I (patients with EAH without obesity) group III (patients with obesity without EAH)								
Lys/Lys	36	63,2	43	78,2	3,0	0,10	0,5	0,21 - 1,1
Lys/Asn	19	33,3	10	18,2	3,3	0,10	2,3	0,94 - 5,36
Asn/Asn	2	3,5	2	3,6	0,0	0,98	1,0	0,13 - 7,09
group II (patients with EAH and obesity) group III (patients with obesity without EAH)								
Lys/Lys	32	54,2	43	78,2	7,3	0,01	0,3	0,15 - 0,74
Lys/Asn	20	33,9	10	18,2	3,6	0,10	2,3	0,98 - 5,46
Asn/Asn	7	11,9	2	3,6	2,7	0,20	3,6	0,77 - 16,49

Analysis of genotype distribution revealed that the homozygous Lys/Lys variant was present in 63.2% of patients in group I and 78.2% of patients in group III. Statistical analysis ($\chi^2 = 3.0$, $p = 0.10$) did not confirm significant differences between the groups, and the odds ratio (OR = 0.5, 95% CI: 0.21–1.1) suggests a potential association of this genotype with EAH;

however, this finding requires further validation. The heterozygous Lys/Asn variant was observed in 33.3% of group I and 18.2% of group III. A trend toward a higher frequency of this genotype in patients with EAH was noted ($\chi^2 = 3.3$, $p = 0.10$, OR = 2.3, 95% CI: 0.94–5.36), which may indicate a possible association with the pathology, though statistical significance was not achieved. The homozygous Asn/Asn variant occurred with equal frequency in both groups (3.5% vs. 3.6%), as evidenced by the absence of differences ($\chi^2 = 0.0$, $p = 0.98$, OR = 1.0), indicating no association of this genotype with EAH (Table 1).

Comparative analysis of genotype distribution demonstrated that the homozygous Lys/Lys variant was present in 54.2% of individuals with EAH and obesity and in 78.2% of individuals with isolated obesity. This difference was statistically significant ($\chi^2 = 7.3$, $p = 0.01$). The calculated odds ratio (OR = 0.3, 95% CI: 0.15–0.74) confirmed a significant reduction in the frequency of this genotype among individuals with EAH. These findings suggest that the homozygous Lys/Lys variant may exert a protective effect in the context of obesity, reducing the likelihood of developing hypertension. The heterozygous Lys/Asn variant was identified in 33.9% of individuals with EAH and obesity (group II) and in 18.2% of individuals with isolated obesity (group III). A trend toward an increased frequency of this genotype in the EAH group was observed ($\chi^2 = 3.6$, $p = 0.10$, OR = 2.3); however, statistical significance was not reached, precluding definitive conclusions regarding a reliable association. The homozygous Asn/Asn variant was recorded in 11.9% of individuals with EAH and obesity and in 3.6% of those with isolated obesity. Analysis of distribution also suggested a potential association of this genotype with EAH in the presence of obesity ($\chi^2 = 2.7$, $p = 0.20$, OR = 3.6), but the results did not achieve statistical significance. Nevertheless, the observed trend suggests that carriage of the Asn allele (in heterozygous or homozygous form) may be associated with an increased risk of developing EAH in individuals with obesity, with an estimated risk increase ranging from 2.7 to 3.6 times.

Analysis of the data presented in Table 2 enabled a detailed investigation of the association between the Lys198Asn polymorphism of the EDN1 gene, its expression levels, and the distribution frequency of various genotypes among patients with specific clinical characteristics. The results revealed patterns in the prevalence of the Lys/Lys, Lys/Asn, and Asn/Asn genotypes, as well as their potential influence on the regulation of ET-1 production, a key mediator of ED. The homozygous Lys/Lys genotype, representing the normal allele, was analyzed first. In group I, comprising patients with AH without obesity, the mean ET-1 concentration in carriers of this genotype was 15.52 ± 4.18 pg/mL. In contrast, in group II, which included patients with AH and obesity, this value was significantly higher, reaching 30.80 ± 9.96 pg/mL. Finally, in group III, consisting of patients with obesity but without AH, the mean ET-1 level was 26.53 ± 5.16 pg/mL.

Table 2. Association of the Lys198Asn polymorphism of the EDN1 gene with its expression levels and genotype distribution in clinical patient subgroups (n=171)

Lys198Asn genotypes of ET-1	**Lys/Lys**	**Lys/Asn**	**Asn/Asn**
The average concentration of ET-1.	group I (n=57)		
	15,52±4,18	24,41±4,91	22,45±1,19
	group II (n=59)		
	30,80±9,96	34,61±11,49	33,59±8,62
	group III (n=55)		
	26,53±5,16	24,13±6,16	30,65±0,07

Subsequent analysis focused on the heterozygous Lys/Asn genotype, characterized by the presence of one mutant allele. In group I, the mean ET-1 concentration in patients with this genotype was 24.41 ± 4.91 pg/mL, notably higher than that observed in Lys/Lys carriers within the same group. In group II, among patients with AH and obesity, this value increased to 34.61 ± 11.49 pg/mL, representing the highest ET-1 level among all genotypes in this subgroup. However, in group III, comprising patients with obesity but without AH, the mean ET-1 concentration decreased to 24.13 ± 6.16 pg/mL, a value comparable to that in group I.

The final stage of the analysis focused on the Asn/Asn genotype, representing homozygosity for the mutant allele. In group I, comprising patients with AH without obesity, the mean ET-1 concentration in carriers of this genotype was 22.45 ± 1.19

pg/mL, slightly lower than that in Lys/Asn heterozygotes but higher than in Lys/Lys carriers within the same subgroup. In group II, which included patients with both AH and obesity, the ET-1 concentration reached 33.59 ± 8.62 pg/mL, remaining elevated but lower than the value observed in Lys/Asn heterozygotes. Notably, in group III, consisting of patients with obesity but without AH, the mean ET-1 level in Asn/Asn carriers was the highest among all genotypes in this subgroup, reaching 30.65 ± 0.07 pg/mL. This observation suggests that homozygosity for the mutant allele may significantly enhance ET-1 expression in the context of obesity, even in the absence of AH.

2. CONCLUSION

Investigating genetic determinants, particularly the Lys198Asn polymorphism of the EDN1 gene, represents a priority in the study of metabolically associated pathologies, including obesity.

Conducting genetic screening for the Lys198Asn polymorphism of the EDN1 gene in high-risk populations, especially among individuals with obesity, offers prospects for developing clinical guidelines and standards for managing patients with cardiovascular pathology.

Identifying carriers of genotypes associated with increased ET-1 expression (Lys/Asn and Asn/Asn) enables the optimization of therapeutic approaches, including the correction of metabolic disorders and targeted interventions for ED, thereby reducing the incidence of complications and improving prognosis.

REFERENCES

[1] Akopyan, A.A., Strazhesko, I.D., Tkacheva, O.N., Esakova, A.P., & Orlova, Ya.A. (2020). Review of gene polymorphisms associated with cardiovascular diseases. Russian Journal of Geriatric Medicine, (4), 333–338.
[2] Bebyakova, N.A., Levitsky, S.N., Shabalina, I.A., & Fadeeva, N.A. (2023). Polymorphism of the endothelin-1 type B receptor gene (EDNRB) and hemodynamic parameters of vascular tone. Modern Issues of Biomedicine, 7(1).
[3] Degnera, E.A., Zueva, V.N., & Khokhlova, D.V. (2022). Influence of polymorphisms in the EDN1 (rs5370), EDNRA (rs6842241), and EDNRB (rs5351) genes on the cardiovascular system. International Scientific Journal "Innovative Science", (5-1), 15–18.
[4] Dymova, O.V. (2018). Modern biomarkers in cardiology. Medical Council, (16), 118–123.
[5] Kostyuk, S.A. (2016). Predictive medicine and genetic testing methods. Medical News, (4), 11–14.
[6] Kostyuk, S.A. (2020). Genes predisposing to multifactorial diseases and genetic polymorphism: What are they? Medical News, (7), 42–46.
[7] Levitsky, S.N., Pervukhina, O.A., & Bebyakova, N.A. (2016). Role of renin-angiotensin system gene polymorphisms in the development of cardiovascular pathology. Bulletin of the Northern (Arctic) Federal University. Series: Medical and Biological Sciences, (4), 30–39.
[8] Ambrosino, P., Bachetti, T., D'Anna, S.E., Galloway, B., Bianco, A., D'Agnano, V., Papa, A., Motta, A., Perrotta, F., & Maniscalco, M. (2022). Mechanisms and clinical implications of endothelial dysfunction in arterial hypertension. Journal of Cardiovascular Development and Disease, 9(5), 136.
[9] Benson, M.D., Yang, Q., Ngo, D., Zhu, Y., Shen, D., Farrell, L.A., Sinha, S., Keyes, M.J., Vasan, R.S., Larson, M.G., Smith, J.G., Wang, T.J., & Gerszten, R.E. (2018). The genetic architecture of the cardiovascular risk proteome. Circulation, 137(11), 1158–1172.
[10] Drożdż, D., Drożdż, M., & Wójcik, M. (2023). Endothelial dysfunction as a factor leading to arterial hypertension. Pediatric Nephrology, 38, 2973–2985.
[11] Muntner, P., Hardy, S.T., Fine, L.J., et al. (2020). Trends in blood pressure control among US adults with hypertension, 1999–2000 to 2017–2018. JAMA: The Journal of the American Medical Association, 324(12), 1190–1200.
[12] Powell-Wiley, T.M., Poirier, P., Després, J.-P., Gordon-Larsen, P., Lavie, C.J., Lear, S.A., Ndumele, C.E., Neeland, I.J., Sanders, P., & St-Onge, M.-P. (2021). Obesity and cardiovascular disease: A scientific statement from the American Heart Association. Circulation.