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The Impact of Lys198Asn Polymorphism of the EDN1 Gene and C786T Polymorphism of the NOS3 Gene on the Pathogenetic Mechanisms of Essential Arterial Hypertension Development in the Context of Obesity

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Abstract This study aims to investigate the contribution of the Lys198Asn polymorphism of the EDN1 gene and the C786T polymorphism of the NOS3 gene to the genetic predisposition to essential arterial hypertension (EAH), taking into account the influence of obesity as a comorbid factor. The analysis did not reveal statistically significant differences in allele and genotype frequencies between the studied groups. However, observed trends suggest a potential role of the Asn allele of the EDN1 gene and the T/T genotype of the NOS3 gene in modulating the risk of developing EAH. The obtained data underscore the need for further research to elucidate the molecular genetic mechanisms underlying the association of these polymorphisms with the pathogenesis of essential hypertension.

Keywords Essential hypertension, Obesity, Genetic polymorphism, EDN1, NOS3

1. Introduction

According to data from the Centers for Disease Control and Prevention (CDC), the epidemiological profile of obesity continues to exhibit a steady upward trend, driven by the complex interplay of genetic, epigenetic, and neuroendocrine factors, as well as modified socio-behavioral determinants [4,5,6]. Projections by the World Health Organization (WHO) indicate that, if current epidemiological trajectories persist, the global prevalence of obesity will reach 18% among men and exceed 21% among women by the year 2025 [8]. This alarming trend underscores the urgent need for a deeper understanding of the multifactorial etiology of obesity and its associated comorbidities, particularly in the context of cardiovascular health.

Contemporary scientific investigations emphasize that obesity represents a polygenic pathological condition, the development of which is determined by a multifaceted interaction of genetic polymorphisms, metabolic dysregulations, and neurohumoral imbalances [1,7,9,10]. The genetic predisposition to obesity and arterial hypertension (AH) is substantiated by molecular genetic studies, which reveal intricate regulatory mechanisms, including variations in gene expression associated with vascular homeostasis. Among these, genes such as *EDN1* (endothelin-1) and *NOS3* (endothelial nitric oxide synthase) play critical roles in modulating vascular tone and endothelial function. Notably, the polymorphism 786 T/C in the *NOS3* gene has garnered significant attention due to its association with endothelial dysfunction and cardiovascular outcomes. This polymorphism, located in the promoter region of the *NOS3* gene, influences the transcriptional activity of endothelial nitric oxide synthase, thereby reducing nitric oxide (NO) bioavailability. Decreased NO levels impair vasodilation and promote oxidative stress, contributing to the pathogenesis of arterial hypertension and increasing the risk of cardiovascular mortality. The 786 T/C polymorphism has been specifically implicated in elevating the risk of mortality in patients with obesity and hypertension, as it exacerbates vascular stiffness and systemic inflammation, further compounding the cardiovascular burden [2,3].

In light of this evidence, obesity is regarded as a major determinant in the pathogenesis and progression of arterial hypertension, exerting a significant impact on the functional activity of the cardiovascular system (CVS). The interplay between obesity and genetic variability, particularly polymorphisms such as 786 T/C in *NOS3*, underscores the necessity for integrating personalized strategies into clinical

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practice. The early identification of genetic risk markers using molecular diagnostic approaches offers a promising avenue for optimizing the prevention and treatment of these interrelated conditions. For instance, genotyping for the 786 T/C polymorphism could enable clinicians to stratify patients based on their risk of adverse cardiovascular events, thereby facilitating targeted interventions such as lifestyle modifications, pharmacological therapies, or closer monitoring of cardiovascular parameters. Moreover, the incorporation of such genetic insights into public health strategies could enhance the efficacy of population-level interventions aimed at curbing the obesity epidemic and its downstream effects on cardiovascular morbidity and mortality [2,3].

In conclusion, the rising prevalence of obesity, coupled with its genetic underpinnings, necessitates a paradigm shift toward precision medicine in the management of obesity-related cardiovascular diseases. The role of the 786 T/C polymorphism in the *NOS3* gene, particularly its contribution to increased mortality risk, highlights the importance of molecular genetic research in elucidating the mechanisms of disease and informing clinical decision-making. By leveraging advances in genomics and personalized medicine, healthcare systems can better address the complex interplay of obesity, arterial hypertension, and cardiovascular risk, ultimately improving patient outcomes.

2. Purpose of the Study

To analyze the role of the Lys198Asn polymorphism of the EDN1 gene and the C786T polymorphism of the NOS3 gene in the predisposition to the development of arterial hypertension among healthy individuals and patients, taking into account the presence or absence of obesity as a concomitant risk factor.

3. Material and Methods of Research

A total of 276 individuals were examined and divided into two groups: the main group (171 patients) and the control group (105 relatively healthy individuals). The main group included patients with a verified diagnosis of essential arterial hypertension (EAH) as well as those without it, stratified according to body mass index (BMI) into individuals with normal body weight and those with obesity. The grouping was designed to assess the influence of obesity on the development and progression of EAH: Group I (patients with EAH without signs of obesity): mean age 61.8 ± 1.46 years (range: 37-71 years); average age of men (n=28) – 60.6 ± 2.27 years (37-71 years), women (n=29) – 63.0 ± 1.60 years (44–73 years); Group II (patients with EAH and signs of obesity): mean age 61.8 ± 1.98 years (range: 44-80 years); average age of men (n=22) – 62.5 ± 2.12 years (46-74 years), women (n=37) – 61.4 ± 3.56 years (33-80 years); Group III (patients with obesity without EAH): mean age 44.5 ± 0.00 years (range: 26-62 years); average age of men (n=12) – 37.1 ± 0.00 years (26-54 years), women (n=43) – 46.6 ± 0.00 years (29–62 years); The control group (n=105) consisted of volunteers matched by sex and age to the main group, but without a family history of arterial hypertension.

The analysis of the association between the polymorphisms of the specified genes and the development of EAH was conducted using the classical epidemiological "case-control" model, which involves a comparative analysis of two independent samples. The quantification of isolated DNA was performed spectrophotometrically using the NanoDrop 2000 device (NanoDrop Technologies, USA) at an absorbance wavelength of A260/280 nm. The purity of all samples, assessed by the A260/280 ratio, met the standard criteria, ranging from 1.7 to 1.8.

4. The Results Obtained and Their Discussion

In the course of a comparative analysis of the allelic distribution of the EDN1 gene among healthy individuals and patients with EAH − both with and without obesity − various genotypes and frequencies were examined in the control and main groups. The results of this analysis are presented in Table 1.

Specifically, the Lys allele was identified in 79.2% of cases within the main group (271 examined alleles), whereas in the control group, its frequency was slightly higher at 83.8% (176 examined alleles). Statistical analysis revealed no significant differences ($\chi^2 = 1.8$, $p = 0.20$), which is supported by the calculated odds ratio (OR = 0.7) and 95% confidence interval (CI: 0.47-1.16). At the same time, the Asn allele was observed at a frequency of 20.8% (71 examined alleles) in the main group and 16.2% (34 examined alleles) in the control group. These differences were also not statistically significant ($\chi^2 = 1.8$, $p = 0.20$), while the OR was 1.4 with a 95% CI of 0.87-2.13, which may indicate a potential trend toward a higher prevalence of this allele in the main group.

Genotypic analysis revealed that the most prevalent variant was Lys/Lys, observed in 64.9% of cases (111 genotypes examined) in the main group and in 70.5% of cases (74 genotypes examined) in the control group. However, these differences were not statistically significant ($\chi^2 = 0.9$, $p = 0.40$), with an odds ratio (OR) of 0.8 (95% CI: 0.46–1.31).

The heterozygous Lys/Asn genotype was recorded in 28.7% of cases (49 genotypes) in the main group and in 26.7% of cases (28 genotypes) in the control group. This difference also lacked statistical significance ($\chi^2 = 0.1$, $p = 0.80$), with an OR of 1.1 (95% CI: 0.64–1.9).

Finally, the Asn/Asn genotype was the least frequent, occurring in 6.4% of cases (11 genotypes) in the main group and in 2.9% of cases (3 genotypes) in the control group. Despite the absence of statistically significant differences ($\chi^2 = 1.7$, $p = 0.20$), 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 (see Table 1).

Table 1. Comparative analysis of the allelic distribution of the Lys198Asn polymorphism of the EDN1 gene among the study groups of patients and healthy individuals (n = 276)

Alleles and Genotypes of Lys198Asn	Number of examined alleles and genotypes				χ2	p	OR	95%CI
	Main group		Control group					
	n	%	n	%				
Lys	271	79,2	176	83,8	1,8	0,20	0,7	0,47 - 1,16
Asn	71	20,8	34	16,2	1,8	0,20	1,4	0,87 - 2,13
Lys/Lys	111	64,9	74	70,5	0,9	0,40	0,8	0,46 - 1,31
Lys/Asn	49	28,7	28	26,7	0,1	0,80	1,1	0,64 - 1,9
Asn/Asn	11	6,4	3	2,9	1,7	0,20	2,3	0,66 - 8,29

Table 2. Differences in the Frequency of Allelic and Genotypic Variants of the C786T Polymorphism in the NOS3 Gene Across the Studied Groups (n = 276)

Alleles and Genotypes of C786T	Number of examined alleles and genotypes				χ2	p	OR	95%CI
	Main group		Control group					
	n	%	n	%				
C	102	29,8	50	23,8	2,4	0,20	1,4	0,92 - 2,01
T	240	70,2	160	76,2	2,4	0,20	0,7	0,5 - 1,09
C/C	20	11,7	9	8,6	0,7	0,50	1,4	0,62 - 3,22
C/T	62	36,3	32	30,5	1,0	0,40	1,3	0,77 - 2,18
T/T	89	52,0	64	61,0	2,1	0,20	0,7	0,42 - 1,14

A comprehensive evaluation of the allelic and genotypic distribution patterns of the C786T polymorphism in the NOS3 gene was also conducted across the studied cohorts using population-genetic analysis methods. The obtained results, reflecting the distribution characteristics of this polymorphic locus according to the clinical and phenotypic features of the examined groups, are presented in Table 2.

The analysis results demonstrated that the frequency of the C allele among the studied alleles in the main group was 102 (29.8%), while in the control group, it was 50 (23.8%). Statistical analysis using the chi-square test ($\chi^2 = 2.4$, $p = 0.20$) revealed no significant intergroup differences. The odds ratio (OR = 1.4, 95% CI: 0.92–2.01) indicated a tendency toward an increased prevalence of the C allele in the main group; however, the absence of statistical significance prevents drawing definitive conclusions regarding its association with the pathological process.

Despite the slightly higher frequency of the C allele in the main group, the data do not allow for a reliable confirmation of its role in the development of EAH. The frequency of the T allele in the main group was 240 (70.2%), compared to 160 (76.2%) in the control group. Nevertheless, statistical analysis ($\chi^2 = 2.4$, $p = 0.20$) did not reveal significant differences between the groups. The odds ratio (OR = 0.7, 95% CI: 0.5–1.09) suggests a trend toward a decreased frequency of the T allele in individuals with EAH, but the lack of statistical significance precludes confirmation of its potential protective role.

Genotypic analysis of the C/C homozygous variant showed a frequency of 11.7% (n = 20) in the main group and 8.6% (n = 9) in the control group. However, the statistical analysis did not identify any significant differences ($\chi^2 = 0.7$, $p = 0.50$), and the odds ratio (OR = 1.4, 95% CI: 0.62–3.22) did not demonstrate a reliable association with EAH.

The frequency of the heterozygous C/T genotype in the main group was 36.3% (n = 62), while in the control group, it was 30.5% (n = 32). Statistical testing revealed no significant difference ($\chi^2 = 1.0$, $p = 0.40$), and the odds ratio (OR = 1.3, 95% CI: 0.77–2.18) indicated a weak trend toward a higher prevalence in individuals with EAH, although this was not statistically confirmed.

The frequency of the T/T homozygous minor genotype was 52.0% (n = 89) in the main group and 61.0% (n = 64) in the control group. No statistically significant differences were observed ($\chi^2 = 2.1$, $p = 0.20$), and the odds ratio (OR = 0.7, 95% CI: 0.42–1.14) indicated a non-significant trend toward a lower prevalence of this genotype among individuals with EAH.

5. Conclusions

Thus, although no statistically significant differences were observed in the distribution of allele variants and genotypes of the EDN1 gene between patients with EAH and healthy individuals, the identified trends (particularly the increased odds ratio for Asn/Asn) warrant further investigation.

The analysis also did not reveal statistically significant differences in the distribution of alleles and genotypes for the C786T polymorphism of the NOS3 gene between the main and control groups ($p > 0.05$ for all comparisons). However, certain trends were identified that require further study: The C allele was more frequent in the main group (29.8% vs.

23.8%), but did not reach statistical significance (p = 0.20); The T allele was less frequent in individuals with EAH (70.2% vs. 76.2%), which may suggest its potential protective role; The T/T genotype was less frequent in individuals with EAH, which could indicate its presumed protective value. Despite the lack of statistically significant differences, the trends in the distribution of alleles and genotypes of C786T suggest a possible role in the regulation of endothelial function. Given the observed trends, it would be reasonable to conduct additional studies aimed at a detailed examination of the impact of the EDN1 and NOS3 gene polymorphisms on the pathogenesis of EAH.

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