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Molecular-Genetic Aspects of Arterial Hypertension Development in Obese Individuals

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Annotation: The aim of the study was to evaluate the frequency of allelic and genotypic variants of the C786T polymorphism of the NOS3 gene in patients with arterial hypertension (AH) and obesity (O), as well as to study their possible role in the development of these pathologies. The study involved 382 people divided into a control group and groups with different combinations of AH and O. Analysis of allele and genotype frequencies showed a tendency to increase the frequency of the C allele in obese patients without AH compared to the control ($p = 0.05$), but no statistically significant differences were found between the other groups. The obtained data suggest a possible involvement of the C786T polymorphism of the NOS3 gene in the pathogenesis of obesity.

Key words: NOS3, C786T polymorphism, arterial hypertension, obesity, genetic predisposition, allele frequency, genotypes

Relevance. Arterial hypertension (AH) and obesity (O) are among the most common chronic diseases of modern society and are among the key risk factors for cardiovascular diseases, including coronary heart disease, stroke, and heart failure [2, 8]. According to the World Health Organization, the prevalence of hypertension in the adult population is about 30-40%, and obesity-more than 20%, with a tendency to increase in recent decades. The combination of these conditions significantly increases the risk of developing metabolic disorders, type 2 diabetesmellitus, and dyslipidemia, which justifies the need for early detection of predisposition to these pathologies [6].

The NOS3 gene (endothelial nitric oxide synthase, eNOS) plays a key role in maintaining vascular homeostasis. It provides the synthesis of nitric oxide (NO) — one of the main vasodilators of the body, which regulates the tone of the vascular wall, thrombosis, endothelial permeability and inflammatory processes in the vascular system. Impaired NO synthesis is one of the leading mechanisms of endothelial dysfunction, which is considered a fundamental link in the development of hypertension and metabolic disorders, including obesity [4, 7].

The C786T polymorphism of the NOS3 gene refers to functional genetic variants that can alter the level of enzyme expression and, consequently, NO synthesis. Studies show that the presence of the C or T allele can affect eNOS activity in different ways, which affects the patient's vascular reactivity and metabolic profile. A number of population-based studies have linked the C786T polymorphism to an increased risk of hypertension, obesity, and cardiovascular complications, but the data remain ambiguous, which may be due to ethnic differences and small sample sizes [3, 5].

Studying the frequency of alleles and genotypes of the C786T polymorphism in various clinical groups, including patients with hypertension, obesity, and their combination, allows us to identify potential genetic markers of risk. This is of practical importance, since knowledge of genetic predisposition can contribute to the early identification of individuals with a high risk of cardiovascular complications and the introduction of personalized preventive and curative measures [1].

Thus, the study of the role of the C786T polymorphism of the NOS3 gene is relevant from the point of view of modern medicine, since it allows combining genetic diagnosis with the assessment of clinical risk factors and can become the basis for developing individualized strategies for the prevention and treatment of hypertension and obesity.

Purpose of the study: to assess the differences in the frequency of allelic and genotypic variants of the C786T polymorphism of the NOS3 gene in patients with hypertension, obesity and their combination in comparison with the control group.

Materials and methods. The study included 382 participants, who were divided into the main and control groups. The main group included 309 patients with various clinical manifestations: 171 patients with arterial hypertension (AH), 138 with obesity (O). The control group consisted of 105 healthy volunteers corresponding to the main group by age and gender, without signs of hypertension, obesity or other chronic diseases of the cardiovascular system.

For a more detailed analysis, the main group was divided into three subgroups:

- **Hypertension without obesity (AH without O)** — patients with confirmed arterial hypertension, but normal body weight;
- **Hypertension with obesity (AH + O)** — patients with a combination of arterial hypertension and obesity;
- **Obese without AH (O without AH)** — patients with obesity, but without arterial hypertension.

The criteria for inclusion in the study were: age 25-65 years, stable course of diseases, voluntary informed consent to participate. Exclusion criteria included the presence of type 1 diabetes, chronic kidney disease, autoimmune diseases, acute inflammatory processes, malignancies, and pregnancy and lactation.

Polymerase chain reaction (PCR) followed by restriction analysis was used to determine the C786T polymorphism of the NOS3 gene. Genetic material was extracted from the patients ' venous blood using standard DNA extraction techniques.

- **PCR:** amplification of a fragment of the NOS3 gene using specific primers.
- **Restriction analysis:** enzymatic cleavage of the amplified product and genotype determination based on differences in the length of the obtained fragments.
- **Quality control:** each sample was analyzed in duplicate, positive and negative controls were used to exclude amplification errors.

The technique allows us to reliably distinguish between three possible genotypes of the C786T polymorphism: **C/C, C/T, and T/T**, which provides an accurate determination of the allele composition in each patient.

The statistical software package SPSS (version 25.0) was used for data analysis.

- **Frequency calculation:** allele and genotype frequencies were calculated as percentages and absolute values for each group and subgroup.
- **Group comparison:** differences between groups were evaluated using the $\chi 2$ (chi-square) criterion. For small subgroup sizes, the Fischer correction was applied.
- **Risk assessment:** to determine the association of polymorphism with clinical conditions, relative risk (RR) and odds ratio (OR) indicators were calculated with 95% confidence intervals. A p-value < 0.05 was considered statistically significant.
- **Additional analysis:** A subgroup analysis was performed to identify associations of the C786T polymorphism with hypertension, obesity, and their combination.

This methodology makes it possible not only to assess the distribution of alleles and genotypes in the study groups, but also to identify possible genetic markers of risk for hypertension and obesity, taking into account the individual genetic characteristics of the participants.

Results. The study included 382 patients, including 309 patients in the main group with various combinations of arterial hypertension (AH) and obesity (O), and 105 patients in the control group.

Subgroups were identified in the main group: AH without obesity (n = 57), AH + O (n = 59) and O without AH (n = 55).

Frequency of alleles and genotypes in the main and control groups

Analysis of the frequency of the C and T alleles of the C786T polymorphism of the NOS3 gene showed that in patients of the main group, the C allele occurred with a frequency of 29.8%, T-70.2%, in the control group C-23.8%, T-76.2%. There were no statistically significant differences between the groups ($\chi2 = 2.4$, $p = 0.20$).

The distribution of genotypes also showed no significant differences: C/C-11.7% vs. 8.6%, C/T-36.3% vs. 30.5%, T/T-52.0% vs. 61.0% ($p > 0.05$ for all comparisons). The values of relative risk (RR) and odds ratio (OR) confirmed the absence of a significant association of polymorphism with general pathology: OR for allele C = 1.4 (95% CI 0.92–2.01), for allele T = 0.7 (95% CI 0.5–1.09).

In the subgroup of patients with hypertension without obesity, the C allele was found with a frequency of 27.2%, the T allele-72.8%. In the AH + O group-C 28.0%, T 72.0%. The differences are statistically insignificant ($\chi2 = 0.0$, $p = 0.90$). The C/C genotype was found in 8.8% and 11.9%, respectively, C/T-36.8% and 32.2%, T/T-54.4% and 55.9% ($p > 0.05$). The OR and RR values indicated that there was no significant association of polymorphism with the combination of hypertension and obesity. The frequency of the C allele was lower in patients with AH without O (27.2%) compared to the "O without AH" group (34.5%), and the T allele was 72.8% versus 65.5%, respectively. The differences did not reach statistical significance ($\chi2 = 1.4$, $p = 0.30$), although there was a tendency to increase the C allele in obese patients without hypertension. Genotypes were distributed as follows: C/C-8.8% and 14.5%, C/T-36.8% and 40.0%, T/T-54.4% and 45.5% ($p > 0.05$). OR for allele C = 0.7 (95% CI 0.4–1.25), allele T = 1.4 (95% CI 0.8–2.5). The frequency of the C allele was 27.2% vs. 23.8% in the control, the T allele was 72.8% vs. 76.2%, $\chi2 = 0.5$, $p = 0.60$. Genotypes C/C — 8.8% vs. 8.6%, C/T-36.8% vs. 30.5%, T/T-54.4% vs. 61.0%. OR and RR also did not indicate a statistically significant relationship (OR for the C allele = 1.2, 95% CI 0.71–2.01). The C allele was found with a frequency of 28.0% in patients with AH + O and 23.8% in controls, the T allele-72.0% vs. 76.2% ($p = 0.50$). Genotypes C/C — 11.9% vs. 8.6%, C/T-32.2% vs. 30.5%, T/T-55.9% vs. 61.0%. There were no statistically significant differences.

In the group of obese patients without hypertension, the frequency of the C allele was 34.5%, and the T allele was 65.5%. In the control group — 23.8% and 76.2%, respectively. The differences reached the borderline level of statistical significance ($\chi2 = 4.2$, $p = 0.05$). OR for the C allele = 1.7 (95% CI 1.02–2.79), OR for the T allele = 0.6 (95% CI 0.36–0.98), which indicates a possible association of the C allele with obesity. Genotypes were distributed as follows: C/C — 14.5% vs. 8.6%, C/T-40.0% vs. 30.5%, T/T-45.5% vs. 61.0%, differences in genotypes are statistically insignificant.

Thus, among all the studied groups**, a statistically significant association was found only in obese patients without hypertension**, who had an increased frequency of the C allele and a reduced frequency of the T allele compared to the control group. No significant differences were found in the subgroups with AH, with AH + O, or when comparing the main group with the control group.

Discussion. The results of the study demonstrate that the C786T polymorphism of the NOS3 gene may be associated with an increased frequency of the C allele in obese patients without hypertension, which is consistent with the hypothesis of the role of endothelial dysfunction in metabolic disorders. The effect of this polymorphism on the development of arterial hypertension in our sample was not confirmed. A limitation of the study is the relatively small size of subgroups, which reduces the statistical power of the analysis. Large-scale population studies are needed to confirm the data obtained.

Conclusions:

1. The C786T polymorphism of the NOS3 gene does not show statistically significant differences in the frequency of alleles and genotypes in patients with AH, AH + O and control.

2. Obese patients without hypertension showed a tendency to increase the frequency of the C allele compared to the control group, which may indicate a possible involvement of this polymorphism in the development of obesity.
3. Further studies on larger samples are needed to clarify the role of the C786T polymorphism of the NOS3 gene in the pathogenesis of cardiovascular and metabolic diseases.

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