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T786C AND GLU298ASP Polymorphisms Of The Nos3 Gene And Their Association With Vascular Dysfunction In Patients With Coronary Heart Disease And Type 2 Diabetes Mellitus

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Abstract: The impact of the T786C and Glu298Asp polymorphisms of the NOS3 gene on vascular reactivity parameters was assessed in patients with coronary artery disease and type 2 diabetes mellitus. Ninety-two patients were examined and genotyping was performed using PCR. Average linear blood flow velocity, arterial diameters before and after the functional test, and resistance and reactivity coefficients were studied. A significant decrease in vascular reactivity was found in carriers of the T/C and Glu/Asp genotypes compared to homozygotes. The identified patterns highlight the importance of NOS3 polymorphisms in the pathogenesis of vascular disorders in the combination of coronary heart disease and type 2 diabetes.

Keywords: Coronary heart disease, type 2 diabetes mellitus, endothelial dysfunction, NOS3 polymorphism.

Introduction:

Coronary heart disease (CHD) and type 2 diabetes mellitus (T2DM) remain the leading causes of morbidity and mortality worldwide. According to the World Health Organization, cardiovascular diseases cause more than 17 million deaths annually, with a significant portion of them associated with coronary heart disease [2]. The presence of type 2 diabetes, characterized by chronic hyperglycemia and metabolic imbalance, significantly aggravates the course of coronary heart disease, accelerating the processes of atherogenesis and leading to the earlier development of complications [3].

Endothelial dysfunction is considered one of the key pathogenetic mechanisms linking diabetes mellitus and coronary heart disease. Impaired production of nitric oxide (NO), a major vasodilator and antiatherogenic factor, leads to deterioration of vascular reactivity, coronary artery spasm, inflammation, and thrombosis[1]. Endothelial NO synthase (eNOS), the enzyme responsible for NO synthesis in the vascular endothelium, is encoded by the NOS3 gene located on chromosome 7q35–36[4-7].

Greatest interest are two polymorphisms of this gene: T786C, located in the promoter region and affecting the transcriptional activity of the gene, and Glu298Asp, leading to the replacement of the amino acid glutamic

acid with aspartic acid in the protein product [11,12]. Both variants have previously been associated with an increased risk of hypertension, ischemic stroke, myocardial infarction, and vascular permeability disorders. However, data on the impact of these polymorphisms on vascular function parameters in patients with a combination of T2DM and coronary artery disease are limited and controversial[8-10].

Modern research emphasizes the need for an integrated approach to the study of molecular genetic factors involved in the pathogenesis of vascular disorders. This is especially relevant for patients with metabolic disorders, in whom vascular complications develop more rapidly and are characterized by greater severity. Establishing a link between genotype and vascular functional parameters can not only deepen our understanding of pathogenesis diseases, but also to promote personalization of prevention and therapy[15].

Thus, the study of the influence of T786C and Glu298Asp polymorphisms of the NOS3 gene on the parameters of endothelial function in patients with coronary heart disease and type 2 diabetes allows us to obtain new data on the molecular mechanisms of the progression of vascular disorders and substantiate the need to take them into account when developing strategies for managing this category of patients.

NOS3 gene polymorphisms, such as T786C in the promoter region and Glu298Asp in exon 7, are associated with altered eNOS expression and activity [13,14]. This may lead to decreased NO production and deterioration of vascular vasodilatory function. Previous studies have demonstrated the role of these polymorphisms in the pathogenesis of hypertension, atherosclerosis, dyslipidemia, and other cardiovascular conditions [18]. However, there is insufficient data on their impact on vascular function in patients with a combination of coronary heart disease and type 2 diabetes, especially given regional characteristics of the population structure and genetic predisposition.

In this regard, it seems relevant to study the relationship between genetic variants of NOS3 and the functional state of the vascular wall in patients with coronary heart disease and type 2 diabetes. Evaluation of such associations will allow us to identify potential molecular markers of vascular complication risk and expand the possibilities of personalized medicine in cardiology and endocrinology.

Objective. To evaluate the influence of T786C and Glu298Asp polymorphisms of the NOS3 gene on vascular reactivity parameters in patients with a combination of coronary heart disease and type 2 diabetes.

Materials and methods

The study included 92 patients with a combination of coronary heart disease (CHD) and type 2 diabetes mellitus, who received inpatient treatment and outpatient observation at the Republican Clinical Hospital No. 1 in Tashkent during 2022–2024. Inclusion criteria included a reliably verified diagnosis of coronary heart disease, confirmed clinically and instrumentally, and a diagnosis of type 2 diabetes according to WHO criteria. Patients were informed of the aims and objectives of the study and signed voluntary consent to participate.

The genetic study involved determining the NOS3 gene polymorphisms T786C and Glu298Asp. The study sample consisted of venous blood, from which DNA was isolated using standard methods and Dianova kits (Russia). Genotyping was performed by polymerase chain reaction (PCR) using CG-1-96 (Corbett Research, Australia) and 2720 (Applied Biosystems, USA) programmable thermal cyclers. Commercial primer kits from Medlab (St. Petersburg) and Litekh (Moscow) were used for amplification and detection, strictly following the manufacturers' protocols.

To assess vascular function, we used duplex ultrasound scanning of the brachial artery with a functional test using reactive hyperemia. The following parameters were determined:

— initial artery diameter (D),
— diameter after the functional test (D1),
— average linear blood flow velocity (Vcp),
— resistance index (Ri),
— pulsatility index (Pi),
— endothelium-dependent vasodilation (EDVD),
— vascular wall reactivity coefficient (K), calculated as the ratio of the change in diameter to the initial value.
— Patients were divided into subgroups based on genotypes:
— by the T786C polymorphism: T/T and T/C;
— by the Glu298Asp polymorphism: Glu/Glu and Glu/Asp.

A comparative analysis was conducted between these groups. All data were processed using the SPSS v.26.0 statistical package (IBM, USA). Distribution was tested using the Shapiro-Wilk test. For normal distributions, Student's t-tests were used; otherwise, nonparametric Mann–Whitney tests were used. The level of statistical significance was set at $p<0.05$. For qualitative variables, χ^2 tests were used.

An additional analysis of possible interactions between

the two studied polymorphisms was also conducted in order to determine their combined effect on vascular reactivity.

Results. When comparing 45 patients with the T/T genotype and 35 patients with the T/C genotype, no statistically significant differences were found in the initial vessel diameters (D), the diameter after the functional test (D1), the resistance index (Ri) and pulsatility (Pi), as well as the endothelium-dependent vasodilation (EDVD) indices. This may indicate the absence of a significant effect of the T786C polymorphism on these parameters under the conditions studied.

However, carriage of the T/C genotype was associated with a significant decrease in mean linear blood flow velocity (Vcp): 38.9±1.19 cm/s versus 43.74±1.41 cm/s in individuals with the T/T genotype (p=0.05), indicating less favorable blood flow conditions. In addition, in the T/C group, an increase in the coefficient (K) characterizing reactive changes in the vascular wall was noted: 0.12±0.015 conventional units versus 0.10±0.011 conventional units in patients with T/T (p=0.01). These changes may reflect a greater susceptibility to dysregulation of vascular tone and reactivity in C allele carriers, potentially contributing to the development or progression of endothelial dysfunction.

Comparison of the Glu/Glu and Glu/Asp groups revealed statistically significant differences in a number of hemodynamic parameters. Glu/Asp genotype carriers, compared with Glu/Glu, showed a significant decrease in vessel diameter after the functional test (D1: 0.33±0.021 cm versus 0.39±0.03 cm; p=0.05), which may reflect a deterioration in endothelium-dependent vasodilation.

In addition, in the Glu/Asp group, a statistically significant decrease in the average linear blood flow velocity was observed (Vcp: 36.9±1.12 cm/s versus 41.57±1.12 cm/s in Glu/Glu; p=0.04), indicating a decrease in hemodynamic efficiency. The resistance indices (Ri) and pulsatility (Pi) did not show significant differences, but a tendency towards a decrease in EDVD was noted in carriers of the Asp allele (4.1±1.4% versus 5.7±1.0%; p=0.08).

An important addition was the significant increase in the coefficient (K), reflecting the reactivity of the vascular wall, in the Glu/Asp group (0.12±0.012 conventional units versus 0.08±0.011 conventional units in Glu/Glu; p=0.01). Thus, the Glu/Asp genotype is associated with adverse changes in the reactive properties of blood vessels and a decrease in blood flow velocity.

Discussion. The results of this study confirm the importance of NOS3 polymorphisms in the pathogenesis of vascular dysfunction in patients with coronary heart disease and type 2 diabetes. The established reliable decrease in the average linear blood flow velocity in carriers of the T/C and Glu/Asp genotypes may indicate a disruption in the synthesis of nitric oxide (NO), a key vasodilator factor produced by the endothelium. This is consistent with literature data indicating an association of these polymorphisms with reduced eNOS expression and decreased NO bioavailability.

An increase in the vascular wall reactivity coefficient (K) in T/C and Glu/Asp carriers indicates increased vascular wall rigidity and impaired adaptive mechanisms, which is critical in patients with high cardiovascular risk [9,17]. Similar results were obtained in a number of previous studies, where NOS3 gene polymorphisms were associated with an increased risk of vascular complications in individuals with metabolic syndrome and diabetes mellitus [20].

It should be noted that the absence of statistically significant differences in vessel diameter and Ri and Pi indices may be associated with compensatory mechanisms and the influence of concomitant therapy, as well as with the limited sample size. Nevertheless, the identified changes in Vcp and K represent potential markers of early vascular regulation disorders in this category of patients.

The obtained results highlight the need to include genetic analysis of NOS3 in a comprehensive assessment of the risk of cardiovascular complications in patients with T2DM and coronary heart disease. Further studies involving larger numbers of patients and longitudinal follow-up will confirm the prognostic value of these markers and their role in a personalized treatment approach.

Conclusion

The study confirmed the presence of significant associations between the T786C and Glu298Asp polymorphisms of the endothelial NO synthase (NOS3) gene and vascular reactivity parameters in patients with coronary artery disease (CAD) and type 2 diabetes mellitus (T2DM). The obtained data demonstrate that carriage of the C allele (T/C genotype) of the T786C polymorphism is accompanied by a decrease in the average linear blood flow velocity and an increase in the vascular reactivity coefficient, this may indicate severe endothelial dysfunction. Similarly, carriage of the Asp allele (Glu/Asp genotype) of the Glu298Asp polymorphism is associated with impaired vascular vasomotor function, manifested by a decrease in the post-load arterial diameter, a decrease in mean blood flow velocity, and increased vascular wall reactivity.

Given the high prevalence of T2DM and coronary heart disease, as well as the complexity of their treatment, determining genetic predisposition to endothelial dysfunction may serve as an important element of a personalized approach to cardiovascular risk assessment. Genotyping for NOS3 polymorphisms can be useful both for stratifying patients by risk of complications and for selecting individual prevention and treatment regimens [9,19].

Further prospective studies with an expanded sample and multivariate analysis are needed to confirm the obtained results and determine the prognostic significance of the studied polymorphisms in clinical practice.

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