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ASSESSMENT OF THE SPECIFIC ASPECTS OF THE GLU298ASP (RS1799983) POLYMORPHISM IN DIABETES COMPLICATED WITH ANGIOPATHY AND IN THE CONTROL GROUP

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Tayanch so‘zlar: eNOS geni, GLU298ASP polimorfizmi (RS1799983), diabetik angiopatiya, oksidlovchi tizim, antioksidant tizim, qon tomir shikastlanishi, nazorat guruhi.
Ключевые слова: Ген eNOS, полиморфизм GLU298ASP (RS1799983), диабетическая ангиопатия, окислительная система, антиоксидантная система, повреждение сосудов, контрольная группа.

Vascular dysfunction is a pathogenetic mechanism linking metabolic disturbances in diabetes mellitus and vascular dysfunction of varying severity. Nitric oxide (NO), a potent vasodilator, antiplatelet agent, and inhibitor of smooth muscle cell proliferation, is a central regulator of endothelial function. This article highlights the importance of the eNOS gene and its polymorphisms in healthy donors used as a control group.

ANGIOPATIYA BILAN ASORATLANGAN DIABETIKLARDA VA NAZORAT GURUHIDA GLU298ASP (RS1799983) POLIMORFIZMINING O‘ZIGA XOS JIHATLARI BAHOLASH

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Qon tomirlar faoliyatining buzilishi qandli diabetdagi metabolizm buzilishlari va turli o‘lchamdagi qon tomirlaridagi buzilishlar orasidagi patogenetik mexanizmdir. Kuchli tomir kengaytirish, antitrombotsitlar agenti va silliq mushak hujayralari proliferatsiyasining tormozlovchisi bo‘lgan azot oksidi (NO) endotelial funktsiyaning markaziy regulyatoridir. Ushbu maqolada nazorat guruhi sifatida olingan sog‘lom donorlarning eNOS geni va polimorfizmining ahamiyati yoritilgan.

ОЦЕНКА СПЕЦИФИЧЕСКИХ АСПЕКТОВ ПОЛИМОРФИЗМА GLU298ASP (RS1799983) ПРИ ДИАБЕТЕ, ОСЛОЖНЕННОМ АНГИОПАТИЕЙ И В КОНТРОЛЬНОЙ ГРУППЕ

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Сосудистая дисфункция является патогенетическим механизмом, связывающим метаболические нарушения при сахарном диабете и сосудистую дисфункцию различной степени тяжести. Оксид азота (NO), мощный вазодилататор, антиагрегант и ингибитор пролиферации гладкомышечных клеток, является центральным регулятором функции эндотелия. В данной статье подчеркивается значение гена eNOS и его полиморфизмов у здоровых доноров, взятых в качестве контрольной группы.

Introduction. A specific genetic trait (the Glu298Asp variant in the eNOS gene) impairs the function of the inner lining of blood vessels (endothelium). In diabetes mellitus, the body requires more nitric oxide (NO) to combat vasoconstriction and platelet aggregation. However, the Asp variant hinders the production of sufficient NO, as the enzyme associated with it becomes less stable. This, in turn, leads to chronic oxygen deficiency in tissues. Among the variations in the studied locus, the G894T (rs1799983) polymorphism, localized in exon 7 of the gene, has the greatest clinical significance. This mutation results in the substitution of glutamic acid (Glu) for aspartic acid (Asp) at position 298 of the amino acid sequence of the protein (Glu298Asp) [4,5,6,8]. The Asp298 variant exhibits increased sensitivity to intracellular proteolysis, resulting in a deficiency of the active enzyme and a decrease in nitric oxide production [1,2,3]. This defect initiates chronic vasospasm and increases the risk of thrombosis. Under conditions of hyperglycemia and oxidative stress, genetically determined NO deficiency triggers the accelerated development of diabetic angiopathy [2,3,5,7].

Objective of the study: To study the significance of the Glu298Asp (rs1799983) polymorphism in the eNOS gene in healthy donors when assessing the development of diabetic angiopathy.

Study Materials and Methods. The study included patients with type 2 diabetes mellitus and healthy donors from whom DNA samples were obtained. Based on clinical and laboratory

testing, the main group included 94 patients registered at Samarkand Medical University. All patients were Uzbeks residing in Uzbekistan. Diagnosis was established based on a combination of clinical, laboratory, and instrumental examination data and was verified according to the international classification. The main group was divided into two subgroups: Group 1 – patients with uncomplicated diabetes mellitus (n=43), Group 2 – patients with diabetes mellitus complicated by diabetic angiopathy (n=51). Molecular genetic testing of biomaterials (DNA) was performed at the Department of Molecular Medicine and Cellular Technologies of the Research Institute of Hematology and Blood Transfusion of the Ministry of Health of the Republic of Uzbekistan.

Study results: In the first group of patients, the wild-type Glu allele (G) was detected in 75.5% of examined patients. This variant is associated with preserved, physiological nitric oxide production. In the control group (n=83), the same Glu allele was detected in 83.1% of cases. It should be noted that in this case, the frequency of the wild-type Glu allele showed a significant decrease in its proportion in the study group; however, no statistically significant differences were found between the compared groups in this sample size ($\chi2$=2.30, p=0.13). The odds ratio was OR=0.62 (95% CI: 0.33–1.15), indicating a tendency toward a protective effect of the Glu allele. The opposite pattern was observed for the minor (mutant) Asp (T) allele. In the study group of patients with angiopathy, its frequency was 24.5%, which is 1.45 times higher than the control group (16.9%). Although the difference did not reach statistical significance (p = 0.13), the odds ratio (OR = 1.60) indicates a significant trend toward an increased risk of angiopathy. The presence of the minor Asp allele of the eNOS genetic marker increases the likelihood of developing vascular complications by 1.6 times compared to the control group (Table 1).

As can be seen from this table, the frequency of the protective homozygous Glu/Glu genotype in the group of patients with angiopathy was 54.9%, which is significantly lower than in the control group (69.9%). This difference corresponds to the level of statistical significance ($\chi2$ = 3.03; p = 0.082). With an odds ratio of 0.5, carriage of the Glu/Glu genotype is associated with a twofold reduction in the risk of developing severe ischemia. A pronounced tendency toward accumulation of heterozygous genotypes was also noted in the study sample. This risk trend was most pronounced in the presence of the heterozygous Glu/Asp genotype of the Glu298Asp polymorphism of the eNOS gene. The frequency of this genotype in Group 1 was 41.2% versus 26.5% in the control group. The risk of developing angiopathy in carriers of the Glu/Asp genotype increases almost twofold (1.94-fold) compared to the control group. This marker is clinically significant, as the $\chi2$ result of 2.98 (95% CI: 0.92–4.08; p=0.084) is statistically significant. Regarding the mutant homozygous Asp/Asp genotype, its frequency in both groups was extremely low (3.9% in Group 1 and 3.6% in the control group). It is likely that homozygous carriage of Asp/Asp is quite rare in the Uzbek population. In the next stage of our study, to assess the marker's specificity, we examined the distribution frequency of alleles and genotypes of the Glu298Asp polymorphism of the eNOS gene between patients in Group 2 (diabetes without angiopathy, n=43) and the control group. When comparing the study groups, the risk of developing angiopathy in diabetes associated with carriage of the Glu/Asp genotype corresponds to an OR value of 1.6. The results of our genotypic distribution analysis confirmed the previously observed trend. In particular, the frequency of the Glu/Glu genotype in the second group was 67.4% (compared to 69.9% in the control group), the heterozygous Glu/Asp genotype was 30.2% (versus 26.5% in the control), and the homozygous Asp/Asp was 2.4% (3.6% in the control). No statistically significant differences in the frequency of any of the genotypes were found between the groups.

1 table.

Carriage of alleles and genotypes of the Glu298Asp polymorphism of the eNOS gene in the subgroup of patients with diabetes mellitus and angiopathy (group 1) and in the control group.

Alleles and genotypes	Number of alleles and genotypes examined				$\chi2$	p	OR	95% CI
	1st group (n=51)		Control (n=83)					
	n	%	n	%				
Glu	77	75.5	138	83.1	2.30	0.130	0.6	0.33 – 1.15
Asp	25	24.5	28	16.9	2.30	0.130	1.6	0.86 – 2.95
Glu/Glu	28	54.9	58	69.9	3.03	0.082	0.5	0.25 – 1.09
Glu/Asp	21	41.2	22	26.5	2.98	0.084	1.9	0.92 – 4.08
Asp/Asp	2	3.9	3	3.6	0.00	0.992	1.1	0.17 – 6.73

Our results shed light on the pathogenesis of vascular complications in diabetes mellitus (DM) and deepen our understanding of their development. Importantly, genetic markers associated with the development of DM itself are not detected in diabetic patients without vascular lesions (angiopathy), unlike healthy individuals. This convincingly demonstrates that the polymorphism under study does not play a role in the development of diabetes. However, the significant genetic differences identified in patients with angiopathy indicate that the Glu298Asp polymorphism acts as a disease progression modifier. Diabetic patients carrying the Asp allele have a significantly worse vascular prognosis. To confirm these observations, we conducted a direct genetic comparison between the first (with angiopathy) and second (without angiopathy) clinical groups. The study revealed statistically significant differences in the frequency of the Glu and Asp alleles, as well as in the distribution of genotypes. In particular, the frequency of the heterozygous Glu/Asp genotype was 36% higher in the first group (41.2%) compared to the second (30.2%). In contrast, the Glu/Glu genotype, associated with protection, was less common in the group with vascular pathology (54.9% versus 67.4%). Comparison of the groups showed that carriage of the Glu/Asp genotype increases the risk of developing angiopathy in diabetes mellitus by 1.6 times (OR = 1.6).

Conclusion. Having the minor Asp allele is associated with a 1.6-fold increased risk of angiopathy, while the Glu/Asp genotype raises this risk to 1.94 times that of controls. These findings support the use of this marker in prognostic panels, alongside a thorough evaluation of other risk factors. Clinically, identifying the Glu/Asp genotype in diabetic patients could enable earlier, targeted therapies for endothelial protection and the reduction of vascular complications.

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