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INFLUENCE OF THE POLYMORPHIC MARKER T-786C OF THE ENOS3 GENE IN DIABETIC NEPHROPATHY

Jabbarov O. O.
Jabbarov Ozimbay Otakhanovich, MD, DSc, Associate Professor,
Head of the Department of Faculty and Hospital Therapy No.2, TMA
Email: dok_azim66@mail.ru

Sapayeva Z. A.
Sapayeva Zulfiya Amangaldiyevna, Assistant of the Department of Internal Diseases and Dermatovenerology, Urgench branch of Tashkent medical academy, Uzbekistan
Email: zulfiyasapayeva89@gmail.com

ANNOTATION

This article presents the results of a study of 129 patients with type 2 diabetes and 110 healthy people to determine whether polymorphic T-786C markers of the ENOS3 gene are associated with the development of diabetic nephropathy. Patients in the main group: 65 patients with a disease duration of up to 10 years, without diabetic nephropathy (33 patients) and with diabetic nephropathy (32 patients), 64 patients with diabetes lasting more than 10-20 years, with no diabetic nephropathy (31 patients) and diabetic nephropathy (33 patients). Genotyping was carried out by polymerase chain reaction. The study showed the association of the C allele and the CC genotype of the ENOS3 gene with a risk of developing diabetic nephropathy in patients with type 2 diabetes mellitus in the studied Uzbek nation.

Keywords: diabetic nephropathy, diabetes mellitus, nitric oxide synthase, endothelin-1,gene, polymorphism,allele, genotype

INTRODUCTION

Nowadays, chronic kidney disease or DN is a pathology that, in terms of the rate of increase in prevalence, is acquiring the character of a non-infectious epidemic, along with diseases such as diabetes mellitus and obesity. DN develops in 13-15% of individuals in the general population and much more often - up to 40-50% - in risk groups, which include patients with type 2 diabetes [2]. According to the forecasts of the International Diabetes Federation, the number of patients with diabetes in the world by 2035 will increase to 587 million people, of which 95% are patients with type 2 diabetes [15].

According to the National Register of Diabetes mellitus, conducted in Uzbekistan in 2007, the cause of death in patients with diabetes was MI in 6.0%, chronic renal failure in 10.8%, and blindness was registered in 1.7%, i.e. the final stages of micro- and macroangiopathies, which lead to severe disability and mortality, develop only in 2-22% of patients with type 2 diabetes [11]. It was found that in patients with newly diagnosed type 2 diabetes, microalbuminuria (MAU) is detected already in 15-40% of cases, proteinuria - in 7-10% and chronic renal failure - in 1%, which reflects the difficulties in diagnosing the disease. With a relatively accurate determination of the onset time of type 2 diabetes, the dependence of the frequency of

development of DN on the duration of the disease is traced the same as in type 1 diabetes: 7-10% with a diabetes duration of 5 years, 20-35% with a duration of 20-25 years, and 50-57% with longer periods of the course of the disease. [7]

In most developed countries of the world, diabetes takes 3-4 place in the structure of mortality, is the leading cause of myocardial infarction, chronic renal failure (CRF), blindness, amputations in the adult population [9, 19]. The mortality rates of patients cause a lot of controversy and are far from true, since these patients die not from diabetes itself, but from diabetes complications and are among the deaths from cardiovascular pathology and chronic renal failure, which significantly reduces the death rate from diabetes.

In recent years, vascular complications of type 2 diabetes have been detected not only in newly diagnosed patients with diabetes mellitus, but even in those with intermediate hyperglycemia. By the time of the clinical manifestation of type 2 diabetes, about 50% of patients already have various macrovascular complications. Consequently, in addition to metabolic, immunological and hemodynamic factors, there are hereditary, molecular genetic factors that determine the development and progression, or vice versa, the protection of vascular complications in diabetes mellitus [16, 18].

The risk of developing nephropathy is definitely genetic. Only about 40-50% of patients with both type 1 diabetes and type 2 diabetes subsequently develop DN. Genetic factors can directly influence the development of DN and / or act in conjunction with genes that influence cardiovascular disease. The search for genetic markers of predisposition or, on the contrary, resistance to diseases is one of the most urgent tasks of medical science. [5]

This is determined by the fact that the establishment of such markers opens up the possibility for clinicians to form risk groups for the development of diseases, and in some pathologies to establish an individual prognosis or diagnosis (including before the clinical manifestation of diseases). Assessment of the role of this or that genetic marker in DM depends on racial and ethnic variations in the frequencies of alleles and genotypes in the studied populations [11, 20].

In recent years, the literature has widely discussed the genetic risk of developing diabetes and its complications, depending on genes for insulin resistance, genes that determine low insulin levels, polymorphism of the angiotensin I-converting enzyme (ACE) gene, and endothelial NO synthase (NOS) gene in patients with both types of diabetes mellitus [1,3,4].

Currently, in the pathogenesis of the development of micro- and macrovascular complications of diabetes, the dominant place is given to endothelial dysfunction, accompanied by a deficiency of vasodilators - nitric oxide (NO), and the activation of local secretion of vasoconstrictors such as endothelin-1 (E-1). Therefore, the gene, endothelial nitric oxide synthase (eNOS3), is of interest as candidate genes for diabetic nephropathy and CKD in type 2 diabetes.

It is known that the endothelium regulates vascular tone through the release of vasodilator and vasoconstrictor factors and modulates the contractile activity of smooth muscle cells.

Endothelial dilatation factors include nitric oxide (NO). NO is the main vasodilator that prevents tonic vascular contraction of neuronal, endocrine or local origin. Under physiological conditions, NO is constantly involved in the adaptation of the vascular system to increased metabolic needs and physical activity. In diseases, an excess of NO is responsible for an increase in peripheral vasodilation, and a deficiency of NO can lead to severe diseases, including arterial

hypertension, ischemic heart disease, and atherosclerosis (also of the vessels of the renal glomerular apparatus). [22.24]

NO prevents platelet adhesion and aggregation, monocyte adhesion, affects the structure of the vessel, which protects the vascular wall and prevents vascular remodeling in various pathological conditions. Nitric oxide is produced by the enzyme NO synthase (NOS). NO synthase exists in three main isoforms, which are named after the type of cells in which they were first found: neuronal NO synthase (nNOS or NOS I), endothelial NO synthase (eNOS or NOS III), and NO synthase macrophages or inducible NO synthase (iNOS or NOSII). Neuronal and endothelial NO synthase are enzymes with stable activity, while the activity of macrophage or inducible NO synthase is more regulated by cytokines. Endothelial NO synthase is stably expressed in endothelial cells. [23]

Inhibition of NO synthase leads to all organic consequences of severe and prolonged arterial hypertension, including atherosclerosis and vascular organ lesions. [21]

The gene for endothelial nitric oxide synthase, eNOS3, is located on the long arm of chromosome 7 (7q36.1) and consists of 26 exons [8]. It has three studied polymorphisms: G894T, 4b/a, and T-786C. It was experimentally established that the presence of allele C at position 786 of the eNOS3 gene promoter leads to a decrease in its activity by 52%, and the resulting lack of eNOS3 is the reason for a decrease in the synthesis and release of NO and endothelial dysfunction [12, 14]. It has been shown that the presence of the C allele and the CC genotype is an independent risk factor for the development of ischemic heart disease, MI in the European and Japanese populations [13,17], as well as the development of DN in patients with type 2 diabetes [10].

It is of interest to study and identify the relationship of eNOS gene polymorphism as a predictor of the development and progression of DN in patients with type 2 diabetes and to determine the genetic determinism of their risk factors in the Uzbek nationality.

Polymorphism of the eNOS gene in type 2 diabetes and its macro and microvascular complications in the Uzbek nationality has not been previously studied.

OBJECTIVE

Assessment of the contribution of the eNOS3 gene polymorphic marker to the risk of developing diabetic nephropathy in type 2 diabetes in Uzbek people.

MATERIAL AND METHODS

In the Republican Scientific and Practical Center of Nephrology on the basis of the III clinic of TMA, the main group of 129 patients with type 2 diabetes was examined and the control group consisted of 110 healthy individuals of the Uzbek nation, included on the basis of the "case-control" principle. Patients in the main group were distributed as follows: 65 patients with a disease duration of up to 10 years, without diabetic nephropathy (33 patients) and with diabetic nephropathy (32 patients), 64 patients with diabetes lasting more than 10-20 years, with no diabetic nephropathy (31 patients) and diabetic nephropathy (33 patients). We studied such indicators as the results of general blood and urine tests, lipid spectrum, glycemic profile, glycosylated hemoglobin, microalbuminuria, glomerular filtration rate (GFR) according to the

CKD-EPI formula, endothelin-1 level in blood plasma, echocardiography, ABPM and Doppler study of renal vessels ...

Testing of the T-786C polymorphism of the ENOS3 gene was carried out on a programmable thermal cycler from Applied Biosystems 2720 (USA), using test systems from Litekh (Russia), according to the manufacturer's instructions.

RESULTS AND ITS DISCUSSION

The frequency of alleles and genotypes of the T-786S polymorphism of the ENOS3 gene in all patients (main group) and the control sample is shown in Figure 1.

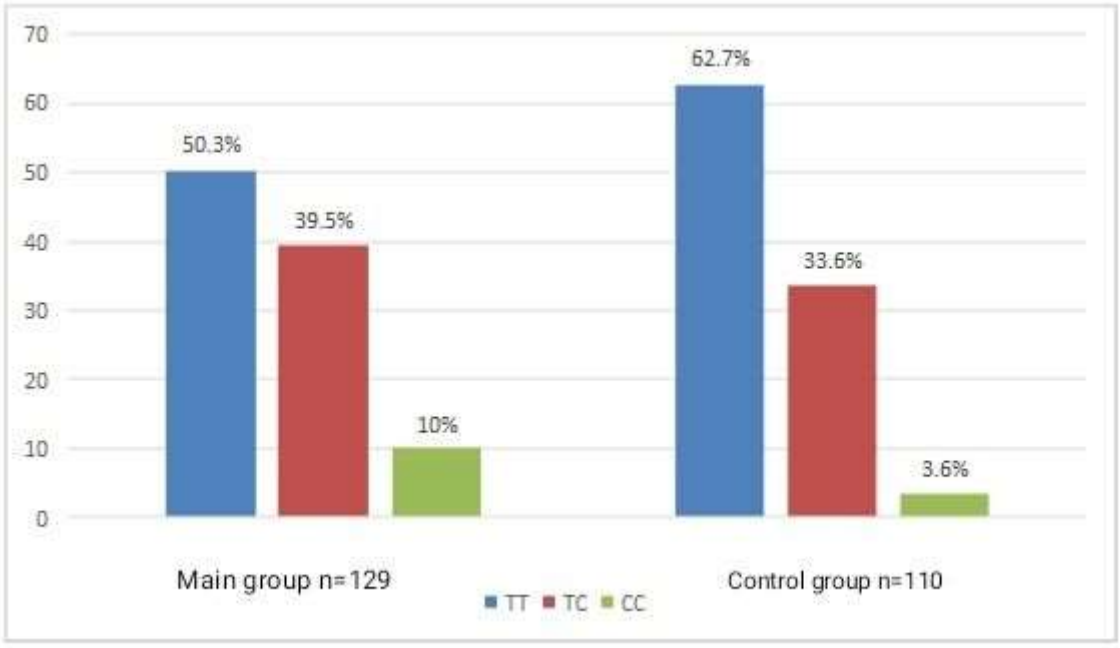

Fig.1 Frequency of distribution of alleles and genotypes of the T-786C polymorphism of the ENOS3 gene in the study and control groups of patients with type 2 diabetes

The prevalence of the T allele in the studied study and control groups was 70.1% and 79.5%, respectively. The incidence of the unfavorable C-allele was 29.8% and 20.4%, respectively. According to statistical calculations, carriers of the C allele have a 1.6 times higher probability of developing the disease than carriers of the T allele ($\chi 2 = 5.5$; $P = 0.02$; OR = 1.6; 95% CI 1.0844 -2.524). Allele T ($\chi 2 = 5.5$; $P = 0.02$; OR = 0.6; 95% CI 0.3962-0.9222) indicates that it has a protective effect on disease progression.

According to the results of the main and control groups, the frequency of distribution of genotypes TT, TC and CC was 50.3%, 39.5%, 10% and 62.7%, 33.6%, 3.6%, respectively. According to statistical calculations, carriers of the CC genotype are 2.9 times more likely to develop the disease than carriers of the TT genotype, and the difference between them has a significant statistical significance ($\chi 2 = 3.7$; $P = 0.05$; OR = 2.9 ; 95% CI 0.9392-9.3906).

The TT genotype was significantly lower in the main group than in the control group, by 50.3%, 62.7%, and showed a protective function against disease progression ($\chi 2 = 3.7$; $P = 0.05$; OR =

0.6 ; 95% CI 0.3594-1.0132). The TS genotype was also significantly lower in the main group than in the control group, 39.5% and 33.6%, respectively, and did not play a significant role in the development of pathology ($\chi 2 = 0.9$; P = 0.3; OR = 1 , 29; 95% CI 0.7592-2.1919).

In our study, we demonstrated an association between the carriage of the C-allele (CC genotype) of the ENOS3 gene and diabetic nephropathy in patients with type 2 diabetes. The results obtained are consistent with the data of domestic and foreign authors, who showed that the carriage of the C-allele is an independent risk factor for DN in patients with type 2 diabetes in various ethnic groups [6]. According to the 2014 meta-analysis, which analyzed the results of 32 studies published before 2013, an association of three eNOS3 gene polymorphisms with the development of DN was revealed: 4b/a, T-786C, and G984T. Polymorphisms 4b/a and T-786C showed a significant association for all genetic models (OR = 1.12-1.77 and 1.11-1.50, respectively). These data and the results of our study allow us to conclude that the eNOS3 gene plays an important role in the development of DN [13] in patients with type 2 diabetes mellitus in the studied Uzbek nation.

CONCLUSION

Thus, the study revealed a significant association of the risk of diabetic nephropathy in patients with type 2 diabetes mellitus with genes encoding endothelial factors (NOS3), whose expression products play a role in the pathogenesis of kidney damage in diabetes mellitus. The results of this study indicate the importance of further study of the molecular basis of the development and progression of DN, which will lead to the development of new promising directions in the prevention of this pathology.

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