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THE ROLE OF THE PPARG2 GENE PRO12ALA POLYMORPHIC MARKER IN THE DEVELOPMENT OF DIABETIC NEPHROPATHY

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Abstract:

This article presents the results of a study of 129 patients with type 2 diabetes and 110 healthy people to determine whether polymorphic Pro12Ala markers of the PPARG2 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.

Keywords: Diabetic nephropathy, diabetes mellitus, PPARG2 gene, polymorphism, allele, genotype

RELEVANCE:

Diabetic nephropathy is considered an urgent medical and social health problem, since it is the main cause of morbidity and mortality caused by chronic kidney disease (CKD), the prevalence of these types of patients is increasing dramatically [1,3,6]. In 2012, the number of new patients requiring renal replacement therapy was 20-35%, and by 2025 it is expected to reach 50-60%. Despite the development of nephrology and diabetology, diabetic nephropathy (DN) is a common complication of diabetes, the prevalence of the disease is 30-40%, according to the analysis of kidney transplantation (dialysis, renal transplantation) in European countries 20-50% of the total number of patients admitted for treatment diabetes mellitus. Diabetes ranks first in the United States, second and third in developed European countries, depending on the need for renal therapy the problem under study [4,10].

A number of studies are being carried out in the world to assess the prognostic value of the clinical, pathogenetic and genetic aspects of the development of diabetic nephropathy in patients with diabetes mellitus. It is necessary to substantiate the prevalence and course of diabetic nephropathy in Uzbek ethnic groups, the influence of metabolic and hemodynamic factors on the development of diabetic nephropathy in groups of patients with impaired renal function; substantiation of the distribution of alleles and genotypes of the T-786C polymorphism of the eNOS3 gene, which affects endothelial dysfunction, in the group of patients with advanced diabetic nephropathy in the Uzbek nation. Distribution of alleles and genotypes of the Pro12Ala polymorphism of the PPARG2 gene encoding the nuclear receptor in groups of patients with advanced diabetic nephropathy, as well as the Leu28Pro polymorphism of the APOE gene, a factor encoding lipid metabolism in patients with diabetic nephropathy, and improving the development of diagnostic algorithms for informational genetic markers the formation and prognosis of risk groups that can contribute to the development of diabetic nephropathy are important [2,7,8].

The PPARG2 gene encodes the nuclear receptor G2, the activation of which induces the expression of many lipogenesis genes and inhibition of lipolysis, which in turn increases the sensitivity of tissues to insulin. The polymorphism of the PPARG2 Pro12Ala gene, leading to a decrease in protein synthesis of this receptor, showed a significant association with the development of diabetic nephropathy in patients with type 2 diabetes [3,5,9].

A number of scientific studies are being conducted to assess the prognostic significance of the clinical, pathogenetic and genetic aspects of the development of diabetic nephropathy in patients with diabetes mellitus, including the effectiveness of first aid based on Amplas primary health care based on neurological studies of diabetic nephropathy (Universitas Sumatera Utara, USA); it turned out that

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this is associated with renal filtration in diabetic nephropathy and a decrease in the microvascular circulatory system (Newcastle University, UK, University of Texas (USA); it has been proven that it is a powerful cytokine in the effective treatment of interleukin-12 (University of British Columbia (Canada); cytomegalovirus infection, which aggravates complications of the central nervous system in diabetic nephropathy, is based on the creation of conditions for severe kidney disease and hemodialysis (University of California, USA), (University of Oslo, Norway); it has been proven that Pro12Ala is a marker of the PPARG2 gene, Pro/Pro, Pro/Ala, Ala/Ala improves diabetic nephropathy [9,10].

Although there is currently a lot of information about the role of various genes involved in the development of DN, there is no consensus on the role of genetic factors in the development of DN. Therefore, research in this area is very important. The development and implementation of new innovative methods for the development of MD in the country is one of the important tasks of the health care system. That is, the use of these innovative methods can predict the risk of disease progression, prolong the period to dialysis, prevent early disability caused by the disease, and reduce mortality.

THE AIM OF THE STUDY:

to assess the distribution of alleles and genotypes of the Pro12Ala polymorphism of the PPARG2 gene encoding a nuclear receptor in a group of patients with the development of DN in the Uzbek nation

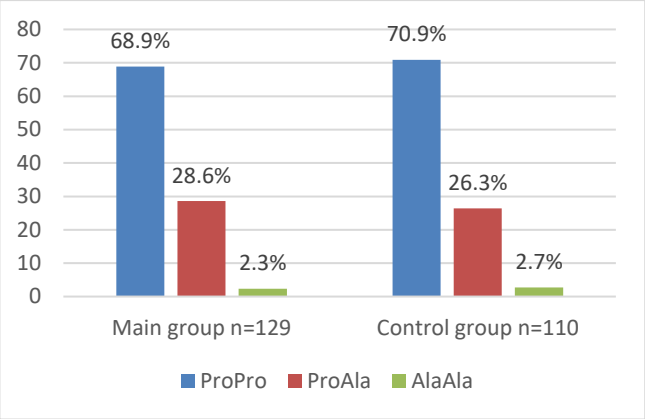
MATERIAL AND METHODS:

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 according to the "case-control" principle. 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 Pro12RAla polymorphism of the PPARG2 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.

For statistical processing of the material, the STATISTICA 6 program was used. The relative risk of disease in carriers of a particular allele and genotype was calculated as an indicator of the odds ratio (OR). The distribution of genotypes was checked for deviations from the Hardy-Weinberg equilibrium. The correlation coefficient r was calculated by the Spearman method. Differences were considered statistically significant at $p < 0.05$.

RESULTS:

In our study, the distribution of genotypes and alleles of the polymorphic marker Pro12RAla in the PPARG2 gene were compared in patients from the main and control groups



The Pro12Ala marker of the PPARG2 gene consists of 3 genotypes Pro/Pro, Pro/Ala, Ala/Ala. In our study, we compared the distribution of genotypes and alleles of the PPARG2 gene of the polymorphic marker Pro12Ala in the main and control groups of patients. The prevalence of the original Pro allele in the studied main and control groups was 83.3% and 83.1%, respectively. The prevalence of the functional Ala allele was 16.6% and 15.9%, respectively. A statistical report showed that carriers of the Ala allele were 1.5 times more likely to develop the disease than carriers of the Pro allele, but the difference was not statistically significant ($\chi 2 = 0.05$; $P = 0.8$; OR = 1.0; 95 % CI 0.6492-1.7214). The old Pro allele did not play a role in the progression of the disease ($\chi 2 = 0.04$; $P = 0.8$; OR = 0.9; 95% CI 0.5809-1.5403). According to the results of the primary and control groups, the prevalence of genotypes Pro/Pro, Pro/Ala, Ala/Ala was 68.9%, 28.6%, 2.3% and 70.91%, 26.36% 2, 73% in year on year. According to the statistical report, carriers of the Ala/Ala genotype did not show any likelihood of developing the disease compared to carriers of the Pro/Pro genotype, and the difference was not statistically significant ($\chi 2 = 0.04$; $P = 0.8$; OR = 0.8 ; 95% CI 0.1679-4.2952). The initial Pro/Pro genotype was significantly lower in the main group than in the control group, 68.9%, 70.91%,

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respectively, and did not show any progression of the disease ($\chi 2 = 0.1$; P = 0.7; OR = 0.9; 95% CI 0.5238-1.5908). It was found that the heterozygous Pro/Ala genotype was slightly more common in the base group than in the control group, and the probability of developing the disease was 1.1 times higher than in the Pro/Pro and Ala/Ala genotypes, but the difference was not statistically significant. ($\chi 2 = 0.2$; P = 0.7; OR = 1.1; 95% CI 0.6349-1.9873). Based on the results of a comparative analysis of alleles and genotypes of the polymorphic marker Pro12Ala of the PPARG2 gene in the main and control groups, it was found that the Ala allele of the functional group in the main group caused the disease 1.05 times more often OR = 1.1 (CI 95% 0.64- 1.72) but did not receive significant statistical significance (P>0.8). Also, the probability of mutation of the homozygous Ala/Ala genotype causing the disease was not observed, OR=0.8 (CI 95% 0.16-4.29) (P> 0.8). It was found that the heterozygous Pro/Ala genotype is 1.12 times more likely to cause the disease OR=1.12 (CI 95% 0.63-1.98), but was not statistically significant (P>0.7). Initial Pro allele OR=0.9 (CI 95% 0.58-1.54), (P>0.8) and Pro/Pro genotypes OR = 0.9 (CI 95% 0.52-1.59) , (P>0.7) showed no protective effect against disease progression.

The frequency of occurrence of the functional allele AlA of the polymorphic modification of the PPARG2 gene of the Pro12Ala PPARG2 gene is 16.6%, OR = 1.1 (CI 95% 0.6492-1.7214) and mutations of the homozygous Ala / Ala genotype in patients with developed DN level 2, 3%, (OR = 0.8 (CI 95% 0.11679-4.2952)).

CONCLUSION:

Thus, the results of our study show that patients with type 2 diabetes mellitus have a high risk of developing diabetic nephropathy for the Ala allelic and heterozygous Pro/Ala genotypes of the PPARG2 gene polymorphic marker.

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