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Association of the Leu28pro Polymorphic Markers of the Apoe and Pro12ala of the Pparg2 Gene in Diabetic Nephropathy in Type 2 Diabetes Patients

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KEYWORDS
gene, polymorphism, allele, genotype, diabetic nephropathy, diabetes mellitus.

ABSTRACT:
This article presents the results of a study of 129 patients with type 2 diabetes and 110 healthy subjects to determine whether the polymorphic markers Leu28Pro of the APOE gene and Pro12Ala of the PPARG2 gene are associated with the development of diabetic nephropathy (DN). Patients in the main group: 65 patients with disease duration 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 that association of Pro allele and Leu/Pro genotype of APOE gene and Ala allele and heterozygous Pro/Ala genotype of PPARG2 gene play significant role in the development of diabetic nephropathy in patients with type 2 diabetes in the studied Uzbek nation.

Introduction.

Diabetic nephropathy (DN) occurs in 13-15% of the general population and is much more common, up to 40-50%, in high-risk groups, which include patients with type 2 diabetes [24,27,30]. The International Diabetes Federation predicts that the number of people with diabetes in the world will increase to 587 million by 2035, 95% of whom will have T2DM [23,27,29].

Diabetic nephropathy is a microvascular complication of diabetes mellitus, the development of which significantly worsens the course and further prognosis of the disease. In DN, the small blood vessels of the filtering apparatus of the kidneys are affected, leading to a further increase in the amount of protein excreted in the urine (proteinuria) [28,25,31,22].

The development of molecular genetic techniques in modern biology makes it possible to reveal in detail the pathobiochemical causes of diseases (congenital, acquired), to use them in diagnosis and to promote new methods of correction in medical practice. "Genetic markers" of diabetes mellitus have shown that a number of diseases can be inherited and a part of the population has the prerequisites for the occurrence of a particular disease. Genes and their protein products that are responsible for the development of such diseases have been discovered. In laboratory practice, these are sometimes referred to as "genetic markers" [26,29,13,21]. The study of such markers makes it possible to identify groups at different risk of developing diseases, and in particular diabetes mellitus. This approach can simplify early diagnosis of the disease (risk of disease development), before the manifestation of the main clinical features. Genetic markers can be used to identify groups of people at risk of developing diabetes [32,8,12].

In recent years, the risk of nephropathy has been definitely determined by genetic factors. Only about 40-50% of patients with both type 1 diabetes and type 2 diabetes subsequently develop DN [24,23,3]. Genetic factors can directly influence the development of DN and/or act together with genes influencing cardiovascular disease. The search for genetic markers of predisposition or, conversely, resistance to disease is one of the most pressing challenges in medical science. [28,18,1,17]. This is due to the fact that the establishment of such markers makes it possible for clinicians to form risk groups for disease development, and for some pathologies to establish an individual prognosis or diagnosis (including before the clinical manifestation of the disease). Evaluation of the role of a particular genetic marker in DM depends on the racial and ethnic variation in allele and genotype frequencies in the populations studied [18,11,4].

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It is of interest to study and identify the relationship between polymorphism of AROE gene and PPARG2 gene as a predictor of the development and progression of DN in patients with type 2 DM and determine the genetic determinism of their risk factors in the Uzbek ethnic group. Polymorphisms of the AROE gene and the PPARG2 gene in type 2 diabetes and its macrovascular and microvascular complications have not been previously studied in the Uzbek ethnic group.

Objective. To assess the contribution of Leu28Pro polymorphic marker of APOE gene and Pro12Ala polymorphic marker of PPARG2 gene in the risk of diabetic nephropathy in type 2 diabetes in Uzbek people.

Material and methods

A core group of 129 patients with type 2 DM and a control group of 110 healthy individuals of the Uzbek nation were examined at the Republican Scientific and Practical Centre of Nephrology, based at the TMA Clinic III. Patients in the main group were distributed as follows: 65 patients with disease duration 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). Indicators such as the results of general blood and urine tests, lipid spectrum, glycemic profile, glycosylated haemoglobin, microalbuminuria, glomerular filtration rate (GFR) using the CKD-EPI formula, plasma endothelin-1 level, EchoCG, CMAD and renal vascular Doppler study.

The Leu28Pro polymorphism of the APOE gene and the Pro12Ala polymorphism of the PPARG2 gene were tested on an AppliedBiosystems 2720 programmable thermal cycler (USA), using Litech test kits (Russia), according to manufacturer instructions.

STATISTICA 6 software was used for statistical processing of the material. The data are presented as mean values with standard deviation (M±SD). Normality of distribution was checked by the Kolmogorov-Smirnov criterion. The relative risk of disease among carriers of a particular allele and genotype was calculated as an odds ratio (OR). The OR value was calculated using an online medical statistics calculator (http:// medstatistic.ru/calculators.html).

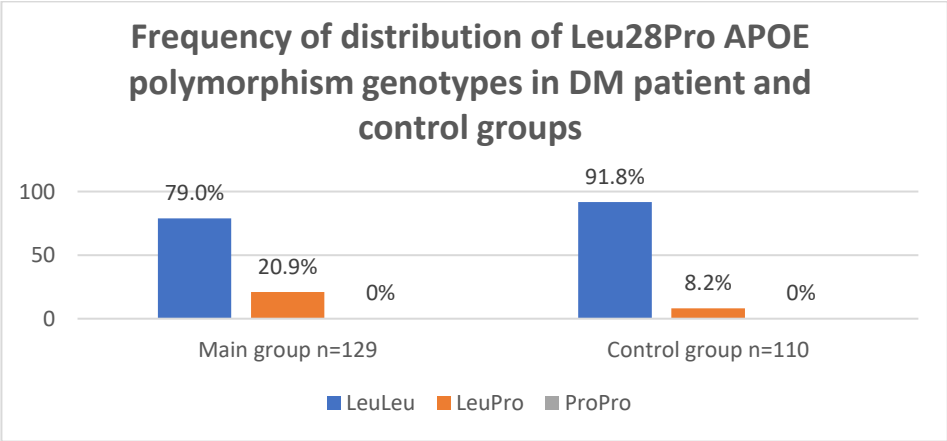
The distribution of genotypes was checked for deviation from Hardy- Weinberg equilibrium. Correlation coefficient r was calculated by Spearman's method. Differences were considered statistically significant at $p<0.05$.

All patients signed an informed consent before the examination.

Results

The allele and genotype frequencies of the Leu28Pro polymorphism of the APOE gene in all patients (main group) and the control sample are shown in Figure 1.

Рис.1



Our study investigated the distribution of genotypes and alleles of the Leu28Pro polymorphic marker of the APOE gene in primary and control patients.

The prevalence of the Leu allele in the main and control groups was 89,5% and 95,95%, respectively. The prevalence of the functional unfavourable allele Pro was 10,4% and 4,1%, respectively. The statistical report shows that Pro allele carriers were 2.7 times more likely to develop the disease than Leu allele carriers, and the difference between them was statistically significant ($\chi 2$ = 6,9; P = 0,008; OR = 2,7; 95% CI 1,2597-5,9608)). The Leu allele indicates that it has a protective effect against disease progression ($\chi 2$ = 6,9; P = 0,008; OR = 0,4; 95% CI 0,1678-0,7938). (Table 1).

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Table 1 Frequency of distribution of alleles and genotypes of the Leu28Pro polymorphism of the APOE gene in the main and control groups of type 2 DM patients.

Allele s and gene types	Number of people surveyed alleles and genotypes				χ^2	P	RR	95% CI	OR	95% CI
	major group N	%	Monitoring N	%						
Leu	31	9,5	11	95,9	6,9278	0,0085	0,9335	0,6203-1,4049	0,3649	0,1678-0,7938
Pro	7	0,4	9	4,1	6,9278	0,0085	2,5581	1,6998-3,8499	2,7403	1,2597-5,9608
Leu/Leu	102	9,0	101	91,8	7,5421	0,006	0,8612	0,5455-1,3597	0,3366	0,1508-0,7515
Leu/Pro	7	20,9	9	8,2	7,5421	0,006	2,5581	1,6202-4,0388	2,9706	1,3308-6,6311
Pro/Pro										

According to the results from the main and control groups, the prevalence of Leu/Leu, Leu/Pro genotypes was 79,0%, 20.9% and 91,8%, 8,2%, but the Pro/Pro genotype was the mutation genotype in our analysis. According to the statistical report, carriers of the Leu/Pro genotype were 2,9 times more likely to have the disease than carriers of the Leu/Leu genotype, and the difference between them was statistically significant ($\chi 2 = 7,5$; P = 0,006; OR = 2,9; 95% CI 1,3308-6,6311).

The Leu/Leu genotype was significantly lower in the main group than in the control group by 79,0%, 91,8% and showed a protective function against disease progression ($\chi 2 = 7,5$; P = 0,006; OR = 0,3; 95% CI 0,1508). - 0,7515). (Tab1e 1).

Our study demonstrated an association between APOE Pro allele (Leu/Pro genotype) carriage and diabetic nephropathy in patients with type 2 diabetes. These results are consistent with those of national and international authors who have shown that carrying the Pro allele is an independent risk factor for DN in patients with type 2 diabetes in different ethnic groups [6].

The allele and genotype frequencies of the Pro12Ala polymorphism of the PPARG2 gene in all patients (main group) and the control sample are shown in Figure 2.

Fig.2

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

The prevalence of the Pro allele in the main and control groups studied was 83,3% and 83,1%, respectively. The prevalence of the abnormal Ala allele was 16,6% and 15,9%, respectively. By statistical calculation, Ala allele carriers were 1,05 times more likely to develop the disease than Pro allele carriers, but the difference was not statistically significant ($\chi2$ = 0,05; P = 0,8; OR = 1,0; 95% CI 0,6492- 1,7214). And the constant Pro allele had a protective effect on disease progression ($\chi2$ = 0,04; P = 0,8; OR = 0,9; 95% CI 0,5809-1,5403).

Table 2 Frequency of distribution of alleles and genotypes of the Pro12Ala polymorphism of the PPARG2 gene in the main and control groups of type 2 DM patients.

Alleles and genotypes	Number of people surveyed alleles and genotypes				χ^2	P	OR	95% CI
	Core group N	%	Control group N	%				
Pro	215	83,3	185	83,1	0,0499	0,8232	0,9459	0,5809-1,5403
Ala	43	16,6	35	15,9	0,0499	0,823	1,0571	0,6492-1,7214
Pro/Pro	89	68,9	78	70,91	0,1036	0,7475	0,9128	0,5238-1,5908
Pro/Ala	37	28,6	29	26,36	0,1597	0,6894	1,1233	0,6349-1,9873
Ala/Ala	3	2,3	3	2,73	0,0391	0,8432	0,8492	0,1679-4,2952

The frequency of Pro/Pro, Pro/Ala, Ala/Ala genotypes were 68,9%, 28,6%, 2,3% and 70,91%, 26,36%, 2,73% in the main and control groups respectively. According to statistical calculation, Ala/Ala genotype carriers did not show any probability of developing the disease compared with Pro/Pro genotype carriers, and the difference between them was not statistically significant ($\chi2$ = 0,04; P = 0,8; OR=0,8; 95% CI 0,11679-4,2952).

The Pro/Pro genotype was significantly lower in the main group than in controls, 68,9%, 70,91% and no predisposition to disease progression was found, but indicating a protective effect on disease progression ($\chi2$ =0,1; P=0,7; OR=0,9; 95% CI 0,5238-1,5908). The heterozygous Pro/Ala genotype was found to be slightly more common in the main group than in the control group, with a 1,1-fold greater probability of disease progression than the Pro/Pro and Ala/Ala genotypes, but the difference was not statistically significant ($\chi2$ = 0,2; P=0,7; OR=1,1; 95% CI 0,6349-1,9873). (Table 2).

Given the frequency of the Ala allele and the heterozygous Pro/Ala genotype in patients with type 2 diabetes mellitus is higher than in controls, the role of this allele and genotype on disease progression, although statistically insignificant, can be thought of.

Discussion

Our study focused on the role of lipid metabolism factor genes, apoprotein E (APOE) and encoding nuclear receptor, PPARG2. As polymorphism of these genes in the development of macro- and microvascular complications in patients with diabetes mellitus type 2 in Uzbek population has not been studied before. Molecular genetic features of type 2 diabetes and their vascular complications in the Uzbek population, as well as issues of effective and safe treatment and early prevention of diabetic nephropathy in type 2 diabetes remain unexplored aspects.

This study examined one of the genes affecting lipid metabolism, the APOE gene, which, as we know, encodes apolipoprotein E. Its main function is to transport cholesterol from sites of synthesis or absorption into tissues. One of the major risk factors for renal pathology is dyslipidaemia [6]. The pathogenetic pathways of dyslipidaemia are based on the general principles of glomerulosclerosis formation.

In our study, genetic testing for alleles and genotypes of the Leu28Pro polymorphic marker of the AROE gene, comparing the main and control groups, revealed that in the main group, the probability of a functionally unfavourable Pro allele was higher OR=2.7 (CI 95% 1.25-5.962). It was noted that the mutant heterozygous Leu/Pro genotype also had a higher probability of trending towards disease OR=2.9

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(CI 95% 1.33-6.63). The mutant monozygotic Pro/Pro genotype was not observed in our study. The wild type allele Leu OR=0.3 (CI 95% 0.16-0.79) and the Leu/Leu genotypes OR=0.3 (CI 95% 0.15-0.75) showed a protective effect against disease development. These rates were repeated in other groups, meaning that there was the possibility of a trend towards disease development in other groups as well.

Analysis of data from foreign studies shows that the e2/eZ/e4 alleles of the AROE gene polymorphic marker are associated with the development of DN, which may indicate an important role of lipid metabolism disorders in the pathogenesis of DN. Japanese authors associated this marker with the progression of renal damage in DM from MAU to proteinuria, where the e2 allele was considered as an independent risk factor for the development of DN [7,10,16].

Chinese researchers conducted a meta-analysis of 29 studies investigating the association of the AROE gene polymorphism with the development of DN. According to these data, the e2/e3 (OR = 1.37), e3/e4 (OR = 1.53) and e4/e4 (OR = 1.86) genotypes are risk factors for the development of DN, while the e3/e3 genotype (the most common genotype in the population) is considered protective. In addition, this meta-analysis found reliable associations with the development of DN [9,15,19].

The reliable associations in the development of DN of this meta-analysis were also confirmed in our study, i.e. we can see that the functionally unfavourable allele Pro of the polymorphic marker Leu28Pro of the APOE gene and mutated heterozygous Leu/Pro genotypes are important in the development of DN in patients of Uzbek ethnicity.

Also, our research work has investigated the role of the PPARG2 gene, one of the major genes, in the development of DN. As the PPARG2 gene encodes a nuclear receptor, it leads to its activation. By expressing many lipogenesis genes and inhibiting lipolysis, it increases tissue sensitivity to insulin. The PPARG2 Pro12Ala polymorphism of the PPARG2 gene is important in the development of diabetes, leading to reduced protein synthesis of this receptor. Mutations in PPARG gene cause insulin resistance syndrome, which is manifested by insulin resistance, dyslipidemia, arterial hypertension. Patients with the Ala/Ala genotype are more prone to obesity [2,5,14,20].

Since 2008, there has been a debate in the literature as to whether this gene is associated with the development of DN or not. It is debated whether this gene affects the hyperglycaemia-induced decrease in GFR or another mechanism of action. The Pro12Ala polymorphism of the PPARG 2 gene has been shown to be significantly associated with the development of type 2 DM. Ala risk allele levels were found to vary from 1-9% in ethnic groups (Asian and African populations) to over 20% in Europeans. Data collected to date show that CKD is a multifaceted complication of diabetes mellitus, and genetic factors play an important role in its origins.

However, in our work, based on the results of genetic testing alleles and genotypes of polymorphic marker Pro12Ala of PPARG2 gene in comparing main and control groups it was found that functionally unfavorable allele Ala in the main group is 1.05 OR=1.1 (CI 95% 0.64-1.72), but did not reach statistically significant significance. The mutation homozygous Ala/Ala genotype was also not associated with disease, OR=0.8 (CI 95% 0.16-4.29). The heterozygous Pro/Ala genotype was 1.12 times more likely to develop the disease, OR=1.12 (CI 95% 0.63-1.98), but did not reach significant statistical significance. The wild-type Pro allele OR=0.9 (CI 95% 0.58-1.54) and Pro/Pro genotypes OR=0.9 (CI 95% 0.52-1.59) showed no protective effect against disease development.

The alleles and genotypes of the polymorphic marker Pro12Ala of the PPARG2 gene in patients of Uzbek ethnicity showed a tendency to the development of DN in the main and control groups, but did not reach statistical significance. Ethnic and gender differences in this polymorphism may be identified when studying a sample of a larger number of patients.

Inclusion of genetic testing in the algorithm of standard methods of examination of patients of Uzbek ethnicity positively affects the pathogenetic mechanism of DN, resulting in the right choice of treatment, early detection of disease complications and, as a consequence, the prevention of disability caused by complications, this process extends the time to hemodialysis and leads to lower mortality rates.

Conclusion

Our study demonstrated an association between carriage of the Pro allele (Leu/Pro genotype) of the APOE gene, the Ala allele (heterozygous Pro/Ala genotype) of the PPARG2 gene and diabetic nephropathy in type 2 DM patients. Obtained results allow concluding that polymorphic marker genotypes leu28pro of APOE gene and Pro12Ala of PPARG2 gene play an important role in the development of DN in patients with diabetes mellitus type 2 in the studied Uzbek nation.

Thus, the study revealed a significant association of the risk of diabetic nephropathy in patients with type 2 diabetes with genes encoding factors of lipid metabolism (APOE) and genes encoding nuclear receptor (PPARG2), whose

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expression products play a role in the pathogenesis of kidney damage in diabetes. The results of this study indicate the importance of further study of the molecular basis of the development and progression of DN will lead to the development of new promising directions in the prevention of this pathology.

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