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The Significance Of The Polymorphic Marker Aluins / Dell> D Of The Ace Gene In The Development Of Diabetic Nephropathy

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Annotation: This article presents the results of a study of 129 patients with type 2 diabetes and 110 healthy people to determine whether the polymorphic markers AluIns / Dell> D of the ACE gene are associated with the development of diabetic nephropathy (DN). 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 using the polymerase chain reaction method. The study showed that the association of the D allele and the heterozygous I/D genotype of the ACE gene play a role in the development of diabetic nephropathy in patients with type 2 diabetes mellitus in the studied Uzbek nation.

Key words: diabetic nephropathy, diabetes mellitus, gene, polymorphism, allele, genotype, angiotensin-converting enzyme, angiotensinogen.

Relevance:

Today, with the increase in the life expectancy of patients with diabetes mellitus (DM), diabetic nephropathy (DN) is becoming an increasingly urgent problem in a series of late complications of diabetes that cause early disability and mortality. 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 [3,11]. It has been established that in patients with newly diagnosed type 2 diabetes, microalbuminuria (MAU) is found in 15–40% of cases, proteinuria — in 7–10%, uremia — in 1%, which reflects the difficulties in the timely diagnosis of type 2 diabetes [1.10].

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. Therefore, 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 [6,8].

As you know, in the pathogenesis of DN, the activation of the local renal renin-angiotensin system (RAS) is of great importance, leading to the development of systemic and intraglomerular hypertension. The mechanism of the pathogenic effect of angiotensin II (AT II) in diabetes mellitus is due not only to vasoconstrictor action, but also to proliferative, prooxidant and prothrombogenic activity, stimulation of the synthesis of cytokines, growth factors. Therefore, the genes encoding the components of the RAS angiotensin converting enzyme (ACE) gene are of interest as candidate genes for diabetic nephropathy in patients with type 2 diabetes.

For the ACE gene, about 20 polymorphic variants are known, the most studied of which is polymorphism due to insertion (presence) or deletion (absence) of an Alu repeat (insertion of a block of 287

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base pairs) in the 16th intron. Increased expression of the ACE gene occurs upon deletion of the Alu repeat (genotype DD). Currently, the association of this polymorphic marker with myocardial infarction (MI) in patients with type 1 and 2 diabetes, arterial hypertension, increased vascular stiffness, with the development of diabetic nephropathy in patients with type 1 diabetes and type 2 diabetes with CKD in various populations has been identified [4,5 , 7.9]. According to the 2011 meta-analysis, they showed a significant association of I/D of the ACE gene with the risk of developing terminal stage of renal failure in type 2 diabetes in the Asian population: D allele: OR = 1.32, DD genotype: OR = 1.67, but in white people, only for DD homozygotes [12]. Most authors consider carriage of the D allele to be an independent risk factor for DN in patients with type 1 and type 2 diabetes in various ethnic groups [13].

Objective:

To assess the contribution of the ACE gene polymorphic marker to the risk of developing diabetic nephropathy in type 2 diabetes in people of Uzbek nationality.

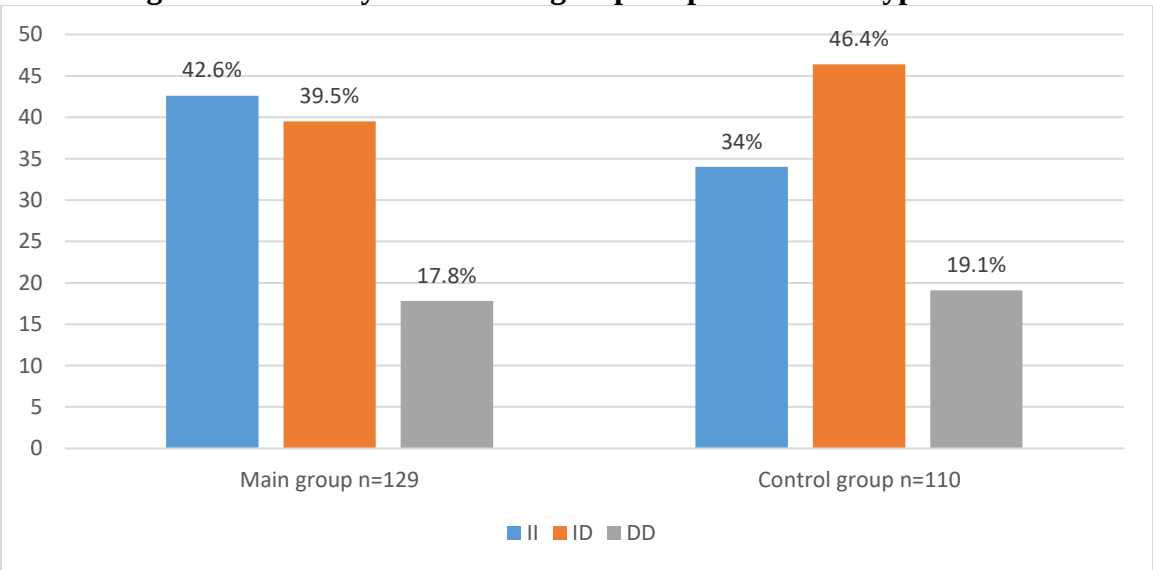
Material and methods:

In the Republican Scientific and Practical Center of Nephrology on the basis of the III clinic of the Tashkent Medical Academy and the private clinic "Global medical center" where the main group of 129 patients with type 2 diabetes were examined and the control group consisted of 110 healthy individuals of the Uzbek nation, included on the basis of the "case- control". 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 AluIns/DelI>D polymorphism of the ACE 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 AluIns / DelI> D polymorphism of the ACE 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 AluIns/Dell>D polymorphism of the ACE gene in the study and control groups of patients with type 2 diabetes.



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In our study, we compared the frequency of distribution of genotypes and alleles of the polymorphic marker AluIns/DelI>D of the ACE gene in patients of the main and control groups. The prevalence of allele I in the studied main and control groups was 62.4% and 57.7%, respectively. The incidence of the unfavorable D allele was 37.5% and 42.3%, respectively. According to statistical calculations, there is no probability of disease progression in carriers of the D allele compared with carriers of the I allele ($\chi 2 = 1.1$; P = 0.3; OR = 0.8; 95% CI 0.57-1.188). Allele I showed a protective effect against disease progression, but no significant differences were found ($\chi 2 = 1.1$; P = 0.3; OR = 1.2; 95% CI 0.842-1.755).

According to the results, the main and control groups, the frequency of distribution of I/I, I/D, D/D genotypes was 42.6%, 39.5%, 17.8 and 34.5%, 46.4%, 19.1 % respectively. According to statistical calculations, carriers of the D/D genotype did not show any likelihood of developing the disease compared to carriers of the I/I genotype ($\chi 2 = 0.1$; P = 0.8; OR = 0.9; 95% CI 0.478-1.771). The I/I genotype was significantly more common in the main group than in the control group, 42.6% and 34.5%, respectively, and showed a 1.4-fold protective effect against disease progression, but there was no significant difference ($\chi 2 = 1.6$; P = 0.2; OR = 1.4; 95% CI 0.833-2.382). Heterozygous genotype I/D was slightly lower in the main group than in the control group, and the probability of disease progression was absent ($\chi 2 = 1.1$; P = 0.3; OR = 0.7; 95% CI 0.452-1.266).

When these groups were examined in groups, for example, in groups that did not develop DN for 10 and 10-20 years, the probability of an unfavorable D allele was OR = 2.9 (95% CI, 1.35 6.45) and was statistically significant (p>0.01). The incidence probability of heterozygous genotype ID was OR = 2.8 (95% CI 0.96-8.46), with significant statistical significance (p>0.05). The probability of a mutation causing a homozygous DD genotype was observed at OR = 2.5 (95% CI 0.587–10.76), but statistically insignificant (p>0.2).

Consequently, the alleles and genotypes of the polymorphic marker AluIns/ DelI>D did not show any predisposition to the disease in the main and control groups, but a tendency towards the development of the disease was observed when comparing between the groups.

The present study has demonstrated an association between the carriage of the D allele (genotype ID) of the ACE 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 D-allele is an independent risk factor for DN in patients with type 1 and 2 diabetes in various ethnic groups [3]. Data from a 2011 meta-analysis showed a significant association of I/D of the ACE gene with the risk of end-stage renal failure in patients with type 2 diabetes in the Asian population [4]. These data and the results of our study allow us to conclude that the ACE gene plays an important role in the development of DN 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 of the renin-angiotensin system (ACE), 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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