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RISK FACTORS FOR THE DEVELOPMENT OF CHRONIC KIDNEY DISEASE

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Abstract

Chronic kidney disease (CKD) is currently the leading cause of disability and mortality in patients with diabetes mellitus (DM). Developing in 40-45% of patients with both insulin-dependent (IDDM) (type I) and non-insulin-dependent (NIDDM) (type II) diabetes, this formidable complication leads to the development of chronic kidney disease and, ultimately, to death from uremia. Kidney damage in diabetes was first described by R. Kimmelstiel and C. Wilson in 1936. Clinically, it is characterized by the following manifestations: increasing proteinuria (with unchanged urinary sediment), arterial hypertension, the development of nephrotic syndrome (in approximately 30% of patients), and a progressive decrease in renal filtration function. The insidiousness of this complication of diabetes is that it develops gradually and remains unnoticed for a long time, since in the initial stages it does not cause discomfort to the patient. In the late stages, when the presence of chronic kidney disease is already established, preventing its further progression is extremely difficult, and often impossible. The results of our study suggest that metabolic, hemodynamic, and genetic factors play a significant role in the development of chronic kidney disease in patients with type 2 diabetes in the study group.

Keywords: Gene, polymorphism, allele, genotype, albuminuria, glomerular filtration rate, renal hemodynamics, chronic kidney disease.

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Introduction

Currently, a direct relationship between the rate of development of chronic kidney disease and the level of carbohydrate metabolism disorders in patients with diabetes has been proven. Hyperglycemia has a damaging effect on glomerular vessels both directly and through the activation of certain biochemical processes. Direct glucotoxicity is associated, in particular, with the fact that high glucose concentrations can have an immediate damaging effect on the vascular endothelium [2,4,11]. Endothelial cells are known to be insulin-independent; therefore, under conditions of hyperglycemia, glucose freely penetrates them, causing dysfunction as a result of pathological metabolic shifts. The glomeruli are the filtering element of the kidneys. They are primarily damaged by diabetes due to high blood sugar levels. These pathological changes in the renal vessels and glomeruli lead to chronic kidney disease [5,9,13]. Chronic kidney disease can persist for a long time without any symptoms or external manifestations. In the early stages of the disease, patients experience hyperfunctional hypertrophy (enlarged glomeruli), increased renal blood flow, and an increased glomerular filtration rate. Several years after the onset of diabetes, the first structural changes in the glomeruli and renal vessels can be detected. Meanwhile, the glomerular filtration rate remains high, and urinary albumin excretion remains within normal limits (less than 30 mg/day) [7,12,15].

Microalbuminuria in chronic kidney disease develops no earlier than five years after the onset of diabetes. It manifests as persistent microalbuminuria. Levels range from 20-200 mg/ml or 30 to 300 mg/day in morning urine. Blood pressure may periodically increase, especially during physical exertion. Further deterioration in CKD patients occurs only in later stages. The pathogenesis of chronic kidney disease is complex [8,14,17]. Chronic kidney disease results from inadequate compensation for carbohydrate metabolism over a long period of time. The metabolic theory of chronic kidney disease posits that persistent hyperglycemia can disrupt all biochemical processes in the kidneys and reduce their functional activity [16,21]. Impaired barrier function of the kidneys leads to the appearance of protein in the urine—proteinuria. If the kidneys stop purifying the blood properly, waste products and water begin to accumulate in the body.

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Urea and creatinine levels in the patient's blood increase, indicating the development of renal failure [10,19,20]. The metabolic and hemodynamic theories attribute the role of the triggering mechanism to hyperglycemia, while the genetic theory attributes it to the presence of a genetic predisposition. Asymptomatic progression of the disease in the early stages leads to a delayed diagnosis of chronic kidney disease in its later stages [1,3,6]. Therefore, annual screening is recommended for all patients with diabetes mellitus to ensure the early detection of chronic kidney disease. Risk factors contributing to the development of chronic kidney disease may include prolonged uncontrolled hyperglycemia, arterial hypertension, excess weight, urinary tract infections, smoking, and male gender. The prognosis of chronic kidney disease depends on the stage of the disease and the timeliness of treatment [6,10].

In understanding the pathogenetic mechanisms of nephrosclerosis development in chronic kidney disease, the analysis of correlations between various factors is of great importance. Thus, the correlation between blood endothelin-1 and other progression factors (hyperglycemia, proteinuria, creatinine and urea levels in the blood) depends on the stage of chronic kidney disease: in the initial stages, the duration and severity of carbohydrate metabolism disorders are of decisive importance, as evidenced by a direct correlation with the duration of diabetes and glycemic levels. In the later stages of the process, damage to the glomerular filter comes to the fore, manifested by increased permeability and deterioration of the excretory function of the kidneys, which is confirmed by a direct correlation with the level of proteinuria, creatinine and urea in the blood [12,13,18]. It is of interest to study and identify the relationship between ACE gene polymorphism as a predictor of the development and progression of chronic kidney disease in patients with type 2 diabetes.

Objective

To assess the role of the AluIns/DelI>D polymorphic marker of the ACE gene in the risk of developing chronic kidney disease and to study the characteristics of the functional state of the kidneys in patients in the early stages of chronic kidney

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disease, as well as to determine the presence of a relationship between them in the early stage of type 2 diabetes development.

Materials and Methods

A total of 129 patients with type 2 diabetes were examined at the Republican Scientific and Practical Center of Nephrology at the III Clinic of the TMA. They comprised the study group and 110 healthy individuals in the control group, recruited according to the case-control principle. Patients in the study group were distributed as follows: 65 patients with a disease duration of up to 10 years, without chronic kidney disease (33 patients) and with chronic kidney disease (32 patients); 64 patients with diabetes for more than 10-20 years, without chronic kidney disease (31 patients) and with chronic kidney disease (33 patients). The following parameters were studied: complete blood count and urine analysis, glycosylated hemoglobin, urea, creatinine, cholesterol, lipid profile, albuminuria, and glomerular filtration rate (GFR) using the CKD-EPI formula, as well as renal vascular resistance. Testing for the Leu28Pro polymorphism of the APOE gene was performed on an AppliedBiosystems 2720 programmable thermal cycler (USA) using Litekh test systems (Russia), according to the manufacturer's instructions.

STATISTICA 6 was used for statistical processing of the material. Data are presented as mean values with standard deviation (M ± SD). Normality of distribution was tested using the Kolmogorov-Smirnov test. The relative risk of disease in carriers of a particular allele and genotype was calculated as the odds ratio (OR). The OR value was calculated using the online calculator of the Medical Statistics program (http://medstatistic.ru/calculators.html). The distribution of genotypes was tested for deviation from Hardy-Weinberg equilibrium. The correlation coefficient r was calculated using the Spearman method. Differences were considered statistically significant at $p < 0.05$.

Results and 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.

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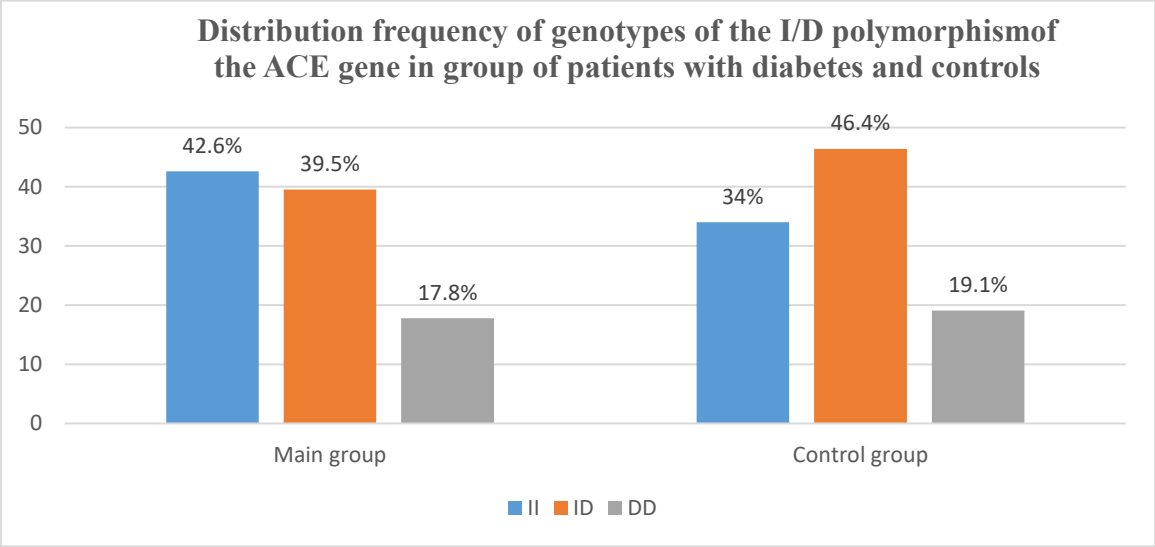

Fig. 1

The prevalence of the I allele in the first and second groups studied was 56.0% and 79.5%, respectively. The frequency of the unfavorable D allele was 43.9% and 20.9%, respectively. According to statistical calculations, the probability of developing the disease was 2.9 times statistically significantly higher in carriers of the D allele than in carriers of the I allele (x2 = 7.6; P = 0.006; OR = 2.9; 95% CI 1.353-6.452). Allele I (x2 = 7.6; P = 0.006; OR = 2.9; 95% CI 1.353-6.452) indicates that it has a protective effect on the progression of the disease.

Table 1 Distribution frequency of alleles and genotypes of the AluIns/DelI>D polymorphism of the ACE gene in the first and third groups of patients with type 2 diabetes

Alleles and genotypes	Number of alleles and genotypes examined				χ^2	P	OR	95% CI
	First group N %		The third group N %					
I	37	56,0	49	79,0	7,652	0,006	0,339	0,155-0,739
D	29	43,9	13	20,9	7,652	0,006	2,954	1,353-6,452
I/I	11	33,3	21	67,7	7,57	0,006	0,238	0,084-0,677
I/D	15	45,4	7	22,5	3,707	0,054	2,857	0,965-8,46
D/D	7	21,2	3	9,6	1,613	0,204	2,513	0,587-10,76

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According to the results, in the first and third groups, the prevalence rates of the I/I, I/D and D/D genotypes were 33.3%, 45.4%, 21.2% and 67.7%, 22.5%, 9.6%, respectively. According to the statistical calculation, carriers of the DD genotype are 2.5 times more likely to develop the disease than carriers of the I/I genotype, and the difference between them has reliable statistical significance (x2 = 1.6; P = 0.2; OR = 2.5; 95% CI 0.587-10.76). Genotype II was significantly lower in the first group than in the third group by 33.3%, 67.7% and showed a protective function against disease progression (x2 = 7.52; P = 0.006; OR = 0.2; 95% CI 0.084-0.677). Genotype I/D was also significantly lower in the third group than in the first group, 45.4% and 22.5%, respectively, and played an insignificant role in the development of pathology (x2 = 0.02; P = 0.9; OR = 1.1; 95% CI 0.529-2.113) (Table 1).

This study demonstrated an association between the Pro allele (Leu/Pro genotype) of the APOE gene and chronic kidney disease in patients with type 2 diabetes. These results suggest that the genotypes of the Leu28Pro polymorphic marker of the APOE gene play a significant role in the development of chronic kidney disease in patients with type 2 diabetes in the study group. The functional state of the kidneys was studied in patients of the 1st, 2nd, 3rd and 4th groups based on the results of AU, urea, creatinine, glycated hemoglobin, GFR, cholesterol and lipid spectrum, and Doppler ultrasound of the renal vessels was also studied.

According to the results of the study comparing groups 1 and 2, compared to group 1, AU was significantly more excreted in the urine in group 2, respectively (32.27 ± 2.47 - 101.56 ± 18.11) ($p<0.05$). The increase in the amount of AU in the urine has a reliable ($p<0.05$) positive correlation with blood creatinine ($r = 0.40$), and GFR ($r = -0.42$) showed an average ($p < 0.05$) negative correlation. When comparing the levels of cholesterol (TC), triglycerides (TGL), and high-density lipoprotein (HDL) in the blood between groups 1 and 2, groups 3 and 4, and groups 1 and 3, no significant changes were observed between them, but when comparing the LDL levels between groups 2 and 4, a significant change was observed ($p < 0.05$). A positive correlation between TC and TGL was observed between groups 1 and 2, respectively ($r=0.26$, $r=-0.68$). Glycated

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hemoglobin was found to have a significant ($p<0.05$) negative correlation with urea, creatinine, and AU ($r = -0.41$, $r = -0.25$) (Table 2).

Table 2 Laboratory results between groups

Laboratory indicators	Group 1	Group 2	Group 3	Group 4
AU	32,27±2,47	101,56±18,11*	325,0±14,49	394,06±21,91*
Urea	4,98±0,23	13,03±0,80*	6,53±0,23	14,37±0,87*
Creatinine	70,86±2,36	248,67±20,25*	81,86±1,83	253,23±24,62*
GFR	90,14±3,17	26,9±72,55*	72,33±2,12	26,65±2,62*
GH	8,75±0,29	8,63±0,36	9,22±0,33	8,15±0,33*
TC	5,50±0,18	5,16±0,10	5,20±0,11	5,49±0,11
TGL	3,51±0,44	3,41±0,18	3,12±0,15	3,37±0,15
LDL	3,07±0,13	3,52±0,07*	3,23±0,09	3,84±0,09*
HDL	1,09±0,03	1,06±0,03	1,04±0,03	1,13±0,03

Note: * - significance ($p<0,05$).

We studied Doppler ultrasonography of the renal vessels and whether there is a relationship between laboratory data. The study showed that an increase in the amount of AU in the urine has a reliable ($p < 0.05$) positive correlation with the resistance index (IR) and the pulse index (PI) of the renal vessels, as well as Vmax ($r = -0.42$), Vmin, and with S/D ($r = -0.43$) showed a reliable ($p < 0.05$) negative correlation. This situation was also noted between groups 3 and 4. It was established that intraglomerular hypertension leads to the development of CKD. (Table 3).

Table 3 Laboratory results between groups

Laboratory indicators	Group 1	Group 2	Group 3	Group 4
Vmax	0,87±0.02	0,77±0.01*	0,79±0,02	0,80±0,01*
Vmin	0,24±0.01	0,17±0.01*	0,18±0,01	0,20±0,01*
IR	0,61±0.01	0,72±0.01*	0,70±0,01	0,74±0,01*
PI	1,60±0.02	1,72±0.01*	1,63±0,02	1,69±0,02*
S/D	3,53±0.06	3,93±0.07*	3,55±0,03	3,75±0,06*

Note: * - significance ($p<0,05$).

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In our study, the negative impact of high glycemia on renal function was assessed by examining serum creatinine, MAU, lipid profile, SCF, and increased renal vascular resistance, both IR and PI. These data and the results of our study allow us to conclude that the genotypes of the AluIns/DelI>D polymorphic marker of the ACE gene play an important role in the development of chronic kidney disease in patients with type 2 diabetes mellitus. The obtained results are consistent with the data of domestic and foreign authors who have shown that carriage of the D allele is an independent risk factor for CKD in patients with type 2 diabetes in various ethnic groups [4,17].

Conclusion

Thus, according to the results of our study, the AluIns/DelI>D polymorphic marker of the ACE gene not only plays a significant role in the development of chronic kidney disease but is also possibly associated with the development of microalbuminuria and a decrease in SCF. Changes in renal function already occur in the microalbuminuric stage of chronic kidney disease. The development of microalbuminuria or a decrease in SCF and an increase in renal vascular resistance (IR and PI), as well as the high frequency of the D allele (I/D genotype) of the AluIns/DelI>D polymorphic marker of the ACE gene in patients with type 2 diabetes, suggest an association between clinical and genetic factors in the early development of chronic kidney disease.

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