ISSN NO: 2770-2936
October 2024

Metabolic And Genetic Aspects of Diabetic Nephropathy

Jabbarov O.O. Doctor of Medical Sciences, Professor,
Tursunova L.D. Ph.D., associate professor,
Khuzhaniyazova N.K.
Tashkent Medical Academy. Nursing Academy.
Tashkent, Uzbekistan

Summary

It is an undeniable fact that in DN caused by T2DM, a clearly defined "preclinical" (latent) stage of development is distinguished, where clinical symptoms are absent, and only functional and laboratory changes characterizing kidney function are detected. It is also undeniable that only early stages of DN can undergo reverse development. The article discusses the clinical and genetic aspects of diabetic nephropathy and their relationship at the early stages of the disease, as well as the combined influence of metabolic and genetic factors on the development of the disease.

The results of our study suggest that the eNOS3 gene plays an important role in the development of DN in patients with type 2 diabetes in the studied Uzbek population.

Keywords: diabetic nephropathy, endothelin-1 gene, polymorphism, allele, genotype, albuminuria, glomerular filtration rate.

Introduction. Diabetic nephropathy (DN) is a specific kidney lesion in diabetes mellitus (DM), characterized by the development of glomerular sclerosis (glomerulosclerosis), leading to impaired kidney function (primarily filtration function) and the development of chronic renal failure. To date, chronic kidney disease or DN is a pathology with a growth rate of prevalence that is taking on the nature of a non-infectious epidemic, along with diseases such as diabetes and obesity. DN develops in 13-15% of the general population and much more frequently - up to 40-50% - in high-risk groups, which include patients with type 2 diabetes [1,2,4]. According to the International Diabetes Federation, the number of patients with diabetes worldwide will increase to 587 million by 2035, with 95% being type 2 diabetes patients [3,11]. Today, DN is the most common cause of end-stage renal failure - nearly 35% of uremic cases [5,7]. The scope of renal involvement in diabetes has increased tremendously in recent years, surpassing even a disease like glomerulonephritis in terms of costs [6,8]. While the number of DN cases in type 1 diabetes has either not changed or decreased in recent years, the incidence of nephropathy in type 2 diabetes has increased by 50% [12,16,19].

In recent years, vascular complications of type 2 diabetes have been detected not only in newly diagnosed diabetes patients but even in individuals with intermediate hyperglycemia. By the time of clinical manifestation of type 2 diabetes, approximately 50% of patients already have various macrovascular complications. Therefore, in addition to metabolic, immunological, and hemodynamic factors, hereditary molecular-genetic factors play a role in determining the development and progression or, conversely, protection against vascular complications in diabetes [14,17].

A classic sign of DN is an increase in urinary protein excretion — microalbuminuria (MAU), followed by proteinuria (PU). The peculiarity of studying kidney complications in patients with type 2 diabetes is the heterogeneity of kidney pathology in this type of disease, which practically does not allow differentiating classical DN based on protein excretion, as in type 1 diabetes [13,15,21]. The leading cause of all vascular complications in diabetes, including chronic kidney disease (CKD), is chronic hyperglycemia. However, in some patients, kidney damage develops and rapidly progresses despite satisfactory glycemic control, indicating the influence of non-glycemic mechanisms. The correlation between proteinuria, blood pressure levels, and the severity of glomerular sclerosis has been demonstrated [9,18].

The leading cause of all vascular complications in diabetes, including CKD, is chronic hyperglycemia. However, in some patients, kidney damage develops and rapidly progresses despite satisfactory glycemic control, indicating the influence of non-glycemic mechanisms. The correlation between proteinuria, blood pressure levels, and the severity of glomerular sclerosis has been demonstrated [10,20].

ISSN NO: 2770-2936
October 2024

It is of interest to study and identify the relationship of the eNOS3 gene polymorphism as a predictor of the development and progression of DN in patients with type 2 diabetes and to determine the genetic determinants of their risk factors in the Uzbek population. The polymorphism of the eNOS3 gene in type 2 diabetes and its macro- and microvascular complications in the Uzbek population have not been previously studied.

Objective. To assess the role of the polymorphic marker of the eNOS3 gene in the risk of developing diabetic nephropathy and to study the peculiarities of kidney functional status in patients at the early stages of DN, as well as to determine the presence of a relationship between them at an early stage of type 2 diabetes in the Uzbek population.

Materials and methods

At the Republican Scientific-Practical Center of Nephrology, based at the III Clinic of TMA, 129 patients with type 2 diabetes and 110 healthy individuals of the Uzbek nation were examined, included based on the "case-control" principle.

The 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, without diabetic nephropathy (31 patients), and with diabetic nephropathy (33 patients).

Testing of the T-786C polymorphism of the eNOS3 gene was carried out using a programmable thermocycler from "AppliedBiosystems" 2720 (USA) with the use of test systems from "Litekh" (Russia), according to the manufacturer's instructions.

Indicators such as the results of general blood and urine tests, glycemic profile, glycated hemoglobin, microalbuminuria, glomerular filtration rate (GFR) using the CKD-EPI formula, the level of endothelin-1 in blood plasma, and parameters of intrarenal hemodynamics - Doppler parameters PIRIVmax - were studied.

For statistical processing of the material, the STATISTICA 6 program was used. Data were presented as mean values with standard deviations (M±SD). The normality of distribution was checked using the Kolmogorov-Smirnov test. The relative risk of disease in carriers of a certain allele and genotype was calculated as an odds ratio (OR). The OR was calculated using the online calculator of the "Medical Statistics" program (http:// medstatistic.ru/calculators.html).

Genotype distribution was tested for deviation from Hardy-Weinberg equilibrium. The correlation coefficient r was calculated using Spearman's method. Differences were considered statistically significant at $p<0.05$.

Results and discussion

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, endothelin-1 and GFR.

According to the results of the study comparing the 1st and 2nd groups, compared with the 1st group, AU was significantly more excreted in the urine in the 2nd group, respectively (32.27±2.47 - 101.56±18.11) ($p<0.05$). An 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 ($r=-0.42$) and endothelin-1 ($r=-0.43$)) showed a reliable ($p<0.05$) negative correlation. Similar results were also observed between the 3rd and 4th groups (Table 1).

Table 1

Laboratory results between groups

Laboratory parameters	Group 1	Group 2	Group 3	Group 4
Duration of the disease	4,42±0,41	4,47±0,42	103,90±0,59	16,15±0,56*
AU	32,27±2,47	101,56±18,11*	325,0±14,49	394,06±21,91*
Endothelin-1	6,72±0,18	4,80±0,26*	5,27±0,21	3,49±0,24*
Urea	4,98±0,23	13,03±0,80*	6,53±0,23	14,37±0,87*

ISSN NO: 2770-2936
October 2024

Creatinine	70,86±2,36	248,67±20,25*	81,86±1,83	253,23±24,62*
GH	8,75±0,29	8,63±0,36	9,22±0,33	8,15±0,33*
GFR	90,14±3,17	26,9±72,55*	72,33±2,12	26,65±2,62*

Note: * - reliability ($p<0.05$).

In understanding the pathogenetic mechanisms of nephrosclerosis formation in diabetic nephropathy, the analysis of correlations between certain factors is of great importance. Thus, the correlation relationships between blood endothelin-1 and other progression factors (hyperglycemia, proteinuria, creatinine and urea levels in the blood) depend on the stage of diabetic nephropathy: at the initial stages, the duration and severity of carbohydrate metabolism disorders are of decisive importance, as evidenced by the direct correlation with the duration of diabetes and the level of glycemia. [12,13].

At the later stages of the process, damage to the glomerular filter comes to the fore, manifested by an increase in its permeability and deterioration in the excretory function of the kidneys, which is confirmed by the direct correlation with the level of proteinuria, creatinine and urea in the blood.

The frequency of alleles and genotypes of the T-786S polymorphism of the ENOS3 gene in all patients (the main group) and the control sample is shown in Table 2.

The prevalence of the T allele in the studied main and control groups was 70.1% and 79.5%, respectively. The frequency of the unfavorable C allele was 29.8% and 20.4%, respectively. According to statistical calculations, the probability of developing the disease in carriers of the C allele is 1.6 times statistically significantly higher than in carriers of the T allele ($\chi2 = 5.5$; $P = 0.02$; OR = 1.6; 95% DN 1.0844-2.524). The T allele ($\chi2 = 5.5$; $P = 0.02$; OR = 0.6; 95% DN 0.3962-0.9222) indicates that it has a protective effect on disease progression.

Table 2

Distribution frequency of alleles and genotypes of the T-786C polymorphism of the NOS3 gene in the main and control groups of patients with type 2 diabetes.

Alleles and genotypes	Number of alleles and genotypes examined				χ^2	P	OR	95% ДИ
	Main group %		Control group N	%				
T	181	70,1	175	79,5	5,5085	0,0189	0,6045	0,3962-0,9222
C	77	29,8	45	20,4	5,5085	0,0189	1,6544	1,0844-2,524
T/T	65	50,3	69	62,7	3,6702	0,0554	0,6035	0,3594-1,0132
T/C	51	39,5	37	33,6	0,888	0,346	1,29	0,7592-2,1919
C/C	13	10,0	4	3,6	3,7283	0,0535	2,9698	0,9392-9,3906

According to the results of the main and control groups, the prevalence of the TT, TC and CC genotypes 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 reliable statistical significance ($\chi2 = 3.7$; $P = 0.05$; 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 ($\chi2 = 3.7$; $P = 0.05$; OR = 0.6; 95% CI 0.3594-1.0132). The TC 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 ($\chi2 = 0.9$; $P = 0.3$; OR = 1.29; 95% CI 0.7592-2.1919) (Table 2).

Our study demonstrated an association between carriage of the C allele (CC genotype) of the ENOS3 gene and diabetic nephropathy in patients with type 2 diabetes.

ISSN NO: 2770-2936
October 2024

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 reliable association of the risk of diabetic nephropathy in patients with type 2 diabetes mellitus with genes encoding endothelial factors (NOS3), the expression products of which play a role in the pathogenesis of kidney damage in diabetes mellitus. Changes in the functional state of the kidneys occur already in the microalbuminuric stage of DN development. The appearance of MAU or a decrease in GFR in a patient with type 2 diabetes indicate an already advanced pathological process in the kidneys from the point of view of the possibility of its reverse development.

Therefore, the search for gene polymorphisms predisposing to the development of DN before the occurrence of complications of the disease, as well as the search for new laboratory and instrumental methods is one of the new promising areas for the prevention of this pathology.

References

1. Железнякова А.В., Лебедева Н.О., Викулова О.К., и др. Риск развития хронической болезни почек у больных сахарным диабетом 2 типа детерминирован полиморфизмом генов *NOS3, APOB, KCNJ11, TCF7L2* // Сахарный диабет. 2014. №3. С. 23-30.

2. Потапов В.А. Поиск генетических маркеров, определяющих предрасположенность к сахарному диабету типа 2. Автореф. дис. канд. мед. наук. Москва – 2010.- 24с.

3. Жаббаров О.О, Саипова Д.С, Эркинова Л.О. Воспаление в диабетической нефропатии.

4. Волчанский, Е. И. Возможности импедансометрии в оценке эндотелиальной дисфункции у больных артериальной гипертензией /

5. Е. И. Волчанский, А. Н. Жидких, М. Е. Стаценко и др. // Пермский медицинский журнал. - 2008. Т. XXV, № 1.С. 49-53.

6. Добронравов В. А. Частота развития микроальбуминурии у больных сахарным диабетом 2 типа / В. А. Добронравов, И. А. Карпова, И. Г. Ковалева, М. Э. Колпакова // Нефрология. - 1999. - Т. 3, № 3. - С. 41-42.

7. Umarova, Z. F., Jabbarov, O. O., Saydaliyev, R. S., Jumanazarov, S. B., & Radjapov, A. B. (2023). DIASTOLIC DYSFUNCTION IN PATIENTS WITH CORONARY ARTERY DISEASE LATE AFTER CORONARY STENTING. *Theoretical aspects in the formation of pedagogical sciences*, *2*(7), 161-164.

8. Рахимова Г.Н., Садыкова А.С., Мухаммедов Р.С., Нурматов Ш.Т. Ассоциация полиморфных маркеров I/D гена ACE с развитием диабетической нефропатии у детей и подростков с СД 1 типа узбекской национальности//Проблемы биологии и медицины.-2007.-1. стр.86-88.

9. Jabbarov, O. O. (2019). Genetic factors of diabetic nephropatia in patients with type 2 diabetes mellitus. *Global journal of medical research*, *1*, 1-7.

10. Бондарь, И. А. Почки при сахарном диабете: патоморфология, патогенез, ранняя диагностика, лечение / И. А. Бондарь, В. В. Климонтов, И. П. Рогова, А. П. Надеев. -М., 2008 - 272 с.

11. Шестакова М.В., Шахмалова М.Ш. Диабетическая нефропатия: клиника, диагностика, лечение. Москва 2009

12. Jumanazarov, S., Jabbarov, O., Umarova, Z., Tursunova, L., & Mirzayeva, G. (2022). Factors affecting platelet hemostasis and resistance to curantil in patients with chronic kidney disease.

13. Alberti G., Zimmet P., Shaw J. IDF. Epidemiology Task fores consensus group. The metabolic syndrome – a new worldwide definition //Lancet. – 2005. – Vol.366 – P. 1059-1062.

14. Jabbarov, O. O. (2019). Genetic factors of diabetic nephropatia in patients with type 2 diabetes mellitus. *Global journal of medical research*, *1*, 1-7.

15. Dellamea B.S., Pinto L.C., Leitao C.B., et. al. Endothelial nitric oxide synthase gene polymorphisms and risk of diabetic nephropathy: a systematic review and meta-analysis // Bio Med Central Medical Genetics. 2014. Vol. 15. P. 9-23.

16. Jabbarov, O. O. (2019). Significance of the RAAS coding component of the ACE gene in the development of diabetic nephropathy in type 2 diabetes. *Infection, immunity and pharmacology*, *6*, 47-55.

ISSN NO: 2770-2936
October 2024

17. Ezzidi I., Mtiraoui N., Mohamed M.B., et al. Association of endothelial nitric oxide synthase Glu298Asp, 4b/a, and -786T>C gene variants with diabetic nephropathy // Journal of Diabetes and its Complications. 2008. Vol. 22, №5. P. 331-338.

18. Жаббаров, О. О., Умарова, З. Ф., Сайдалиев, Р. С., Турсунова, Л. Д., Хужаниязова, Н. К., Кодирова, Ш. А., & Надирова, Ю. И. (2023). ИЗУЧЕНИЕ ВЛИЯНИЯ РАЗЛИЧНЫХ ГЕНОВ НА РАЗВИТИЕ ДИАБЕТИЧЕСКОЙ НЕФРОПАТИИ ПРИ САХАРНОМ ДИАБЕТЕ 2 ТИПА.

19. Nakayama M., Yasue H., Yoshimura M., et al. T(- 786)C mutation in the 5'-flanking region of the endothelial nitric oxide synthase gene is associated with myocardial infarction, especially without coronary organic stenosis // American Journal of Cardiology. 2000. Vol. 86, №6. P. 628-634.

20. Poirier O., Mao C., Mallet C., et al. Polymorphisms of the endothelial nitric oxide synthase gene - no consistent association with myocardial infarction in the ECTIM study. Eur J ClinInvest. 1999 Apr;29(4):284-90.

21. Mirzayeva, G. P., Jabbarov, O. O., Umarova, Z. F., Qodirova Sh, I., Tursunova, L. D., Nadirova Yu, I., & Rahmatov, A. M. (2023). Assessment of Efficacy and Optimization of Antiplatelet Therapy in Patients with Ischemic Heart Disease.