European Journal of Interdisciplinary Research and Development
Volume- 45 November- 2025
Website: www.ejird.journalspark.org ISSN (E): 2720-5746

CLINICAL AND GENETIC FACTORS IN THE DEVELOPMENT OF DIABETIC NEPHROPATHY

Jabbarov O. O.
Khuzhaniyazova N. K.
Tursunova L. D.
Erkinova L. O.
Tashkent State Medical University
Nursing Academy, Clinic Asl shifo. Tashkent, Uzbekistan

Annotation
Diabetic nephropathy is a specific pathological change in the renal vessels that occurs in diabetes mellitus. This complication leads to glomerulosclerosis, reduces renal filtration function, and contributes to the development of chronic renal failure (CRF). Clinically, diabetic nephropathy is manifested by proteinuria and microalbuminuria, nephrotic syndrome, arterial hypertension, signs of uremia, and CRF. Diabetic nephropathy is one of the most severe complications of both type 1 and type 2 diabetes mellitus. It manifests in the late stages of the disease and is a leading cause of death. Diabetic nephropathy is diagnosed in 10-20% of patients with diabetes. The peak development of diabetic nephropathy occurs 15-20 years after the onset of diabetes.
The results of our study suggest that metabolic, hemodynamic, and genetic factors play a significant role in the development of diabetic nephropathy in patients with type 2 diabetes in the study group.

Keywords: Albuminuria, glomerular filtration rate, renal hemodynamics, diabetic nephropathy, gene, polymorphism, allele, genotype.

Introduction

As is well known, the kidneys in the human body are responsible for purifying the blood of toxins, harmful substances, and toxic waste products. After this filtration, all waste products are eliminated from the body in urine.
The renal glomeruli are the filtering elements 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 diabetic nephropathy.
Currently, there is a generally accepted classification of diabetic nephropathy by stages, according to which the following are distinguished: the microalbuminuria stage, the proteinuria stage, and the chronic renal failure stage [1,2,9]. Diabetic nephropathy proceeds for a long time without any symptoms or external manifestations. In the initial stage of the disease, the patient experiences hyperfunctional hypertrophy (an increase in the size of the renal glomeruli), increased renal blood flow, and an increase in the glomerular filtration rate. Several years after the onset of diabetes mellitus, the first structural changes in the renal glomeruli and renal vessels

can be detected. At the same time, the glomerular filtration rate remains high, and albumin excretion in the urine remains within normal limits (less than 30 mg/day) [5,11,15].

Microalbuminuria in diabetic nephropathy 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 patients with diabetic nephropathy occurs only in later stages. The pathogenesis of diabetic nephropathy is complex [7,14,17].

There are several theories explaining the cause of diabetic nephropathy: metabolic, hemodynamic, and genetic. Despite their differences, most experts agree that the main factor and trigger for the development of diabetic nephropathy is hyperglycemia [8,12]. Diabetic nephropathy is a consequence of inadequate compensation for carbohydrate metabolism disorders over a long period of time. The metabolic theory of diabetic nephropathy states that persistent hyperglycemia can lead to disruption of all biochemical processes in the kidneys and a decrease in their functional activity. Impairment of the "barrier" function of the kidneys leads to the appearance of protein in the urine - proteinuria. If the kidneys stop purifying the blood properly, metabolic products and water begin to accumulate in the body. Urea and creatinine levels in the patient's blood increase, indicating the development of renal failure [4,13,16].

The metabolic and hemodynamic theories attribute hyperglycemia as the trigger, while the genetic theory attributes it to a genetic predisposition. Asymptomatic progression of the disease in the early stages leads to a delayed diagnosis of diabetic nephropathy in its later stages. Therefore, annual screening is recommended for all patients with diabetes to ensure early detection of diabetic nephropathy. Risk factors contributing to the development of diabetic nephropathy may include prolonged uncontrolled hyperglycemia, hypertension, excess weight, urinary tract infections, smoking, and male gender. The prognosis of diabetic nephropathy depends on the stage of the disease and the timeliness of treatment [6,10].

In understanding the pathogenetic mechanisms of nephrosclerosis development in diabetic nephropathy, 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 diabetic nephropathy: 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 the level of glycemia. 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 the APOE gene polymorphism as a predictor of the development and progression of DN (diabetic nephropathy) in patients with type 2 diabetes.

Objective:

To study the role of metabolic, hemodynamic and genetic (Leu28Pro polymorphic marker of the APOE gene) factors in the development of diabetic nephropathy, their interrelationships, and their impact on disease progression.

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 Uzbek individuals, who formed a case-control group. Patients in the study 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 for more than 10-20 years, without diabetic nephropathy (31 patients) and with diabetic nephropathy (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. Testing for the Leu28Pro polymorphism of the APOE gene was performed on an AppliedBiosystems 2720 programmable thermal cycler (USA) using Litekh test kits (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

Renal function was assessed in patients in Groups 1, 2, 3, and 4 using AU, urea, creatinine, glycated hemoglobin, GFR, cholesterol, and lipid profile measurements. Doppler sonography of the renal vessels was also performed.

A study comparing Groups 1 and 2 showed that AU was significantly more excreted in the urine in Group 2 than in Group 1 (32.27±2.47 vs. 101.56±18.11) ($p<0.05$). Increased AU in urine had a significant ($p<0.05$) positive correlation with blood creatinine ($r=0.40$), while GFR ($r=-0.42$) showed a moderate ($p<0.05$) negative correlation.

When comparing the levels of cholesterol (CHT), 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 levels of LDL 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 hemoglobin was found to have a significant ($p < 0.05$) negative correlation with urea, creatinine, and AU ($r = -0.41$, $r = -0.25$) (Table 1).

Table 1 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*
ГГ	8,75±0,29	8,63±0,36	9,22±0,33	8,15±0,33*
CHT	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, as 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 pulse index (PI) of the renal vessels, and Vmax ($r = -0.42$), Vmin and with S / D ($r = -0.43$) showed a reliable ($p < 0.05$) negative correlation (Table 2).

Table 2 Результаты лабораторных показателей между группами

Laboratory indicators	Group 1	Group 2	Group 3	Group 4
АУ	32,27±2,47	101,56±18,11*	325,0±14,49	394,06±21,91*
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).

A similar situation was observed between groups 3 and 4. It was established that intraglomerular hypertension leads to the development of DN (Table 2).

Our study examined the genotype and allele distribution of the Leu28Pro polymorphic marker of the APOE gene in study and control patients.

The prevalence of the Leu allele in the study and control groups was 89.5% and 95.9%, respectively. The prevalence of the functionally unfavorable Pro allele was 10.4% and 4.1%, respectively. Statistical analysis shows that carriers of the Pro allele are 2.7 times more likely to develop the disease than carriers of the Leu allele, and the difference between them is statistically significant ($\chi2 = 6.9$; $P = 0.008$; $OR = 2.7$; 95% CI 1.2597-5.9608). The Leu allele indicates that it has a protective effect against disease progression. ($\chi2 = 6.9$; $P = 0.008$; $OR = 0.4$; 95% CI 0.1678-0.7938).

Table 3 Distribution frequency of alleles and genotypes of the Leu28Pro polymorphism of the APOE 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% CI
	Main group n	%	Control group n	%				
Leu	31	89,5	11	95,9	6,9278	0,0085	0,3649	0,1678-0,7938
Pro	7	10,4	9	4,1	6,9278	0,0085	2,7403	1,2597-5,9608
Leu/Leu	102	79,0	101	91,8	7,5421	0,006	0,3366	0,1508-0,7515
Leu/Pro	7	20,9	9	8,2	7,5421	0,006	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 mutation genotype Pro/Pro was not found in our analysis. According to the statistical report, the probability of the disease in carriers of the Leu/Pro genotype is 2.9 times higher than in carriers of the Leu/Leu genotype, and the difference between them is statistically significant. ($\chi2$ = 7.5; P = 0.006; OR = 2.9; 95% CI 1.3308-6.6311). The Leu/Leu genotype was significantly lower in the study group than in the control group by 79.0%, 91.8% and showed a protective function against disease progression ($\chi2$ = 7.5; P = 0.006; OR = 0.3; 95% CI 0.1508 -0.7515). (Table 3).

This study demonstrated an association between the Pro allele (Leu/Pro genotype) of the APOE gene and diabetic nephropathy 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 diabetic nephropathy in patients with type 2 diabetes in the study group.

Conclusion

Thus, changes in renal function occur already in the microalbuminuric stage of diabetic nephropathy. The appearance of MAU or a decrease in SCF and an increase in renal vascular resistance (IR and PI), as well as the high frequency of the Pro allele (Leu/Pro genotype) of the Leu28Pro polymorphic marker of the APOE gene in patients with type 2 diabetes, suggest an association between metabolic, hemodynamic, and genetic factors in the early development of diabetic nephropathy.

References

1. Koopal, C. Influence of APOE-2 genotype on the relation between adiposity and plasma lipid levels in patients with vascular disease / C. Koopal, Y. van der Graaf, F. Asselbergs, J. Westerink, F. Visseren // Int J Obes Relat Metab Disord. – 2015. - Vol. 39. - № 2. - P. 265–269.

2. Tursunova, L., & Jabbarov, O. O. (2024). The role of renal vascular dopplerography in the diagnosis of chronic kidney disease. *Медицинский журнал молодых ученых*, (12 (12)), 52-57.

3. Дедов И. И. Диабетическая нефропатия / И. И. Дедов, М. В. Шестакова. - М. : Универсум Паблишинг, 2000. - 240 с.
4. Jabbarov, O. O., Daminov, B. T., & Tursunova, L. D. (2019). Роль метаболических факторов в прогрессировании диабетической нефропатии. *Вестник Ташкентской медицинской академии*, *4*, 25-29.
5. Villeneuve, S. The potential applications of Apolipoprotein E in personalized medicine / S. Villeneuve, D. Brisson, N. Marchant, D Gaudet // Frontiers in Aging Neuroscience. – 2014. - Vol. 154. – P. 3-6.
6. Сапаева, З. А., Жаббаров, О. О., Кадирова, Ш. А., & Ходжанова, Ш. И. (2019). ВЛИЯНИЕ АНТИГИПЕРТЕНЗИВНЫХ ПРЕПАРАТОВ НА ПОКАЗАТЕЛИ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ У БОЛЬНЫХ С СИСТЕМНОЙ КРАСНОЙ ВОЛЧАНКИ. *Экономика и социум*, (10 (65)), 266-271.
7. Rodrigues, A. Genetic variants in genes related to lipid metabolism and atherosclerosis, dyslipidemia and atorvastatin response / A. Rodrigues [et al.] // Clinica Chimica Acta. – 2013. – Vol. 417. – P. 8-11.
8. Рахматов, А., Жаббаров, О., Қодирова, Ш., Жуманазаров, С., Мирзаева, Г., & Тожибоев, М. С. (2022). Подаграда буйраклар зарарланишининг клиник ва генетик хусусиятлари.
9. 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.
10. Сапаева, З. А., Жабборов, О. О., Максудова, М. Х., Ходжанова, Ш. И., & Кадирова, Ш. А. (2019). ОСОБЕННОСТИ СУТОЧНОГО ПРОФИЛЯ АРТЕРИАЛЬНОГО ДАВЛЕНИЯ У БОЛЬНЫХ СИСТЕМНОЙ КРАСНОЙ ВОЛЧАНКОЙ С НАЛИЧИЕМ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ. *Кардиоваскулярная терапия и профилактика*, *18*(S1), 132-133.
11. Маслова О.В., Сунцов Ю.И., Шестакова М.В., Казаков И.В., Викулова О.К., Сухарева О.Ю., Мартынов С.А., Трубицына Н.П. Распространенность поражения почек при сахарном диабете 1 и 2 типов в Российской Федерации // Сахарный диабет – 2009 - № 4. - С. 47-51.
12. Jabborov, O. O. (2019). Features of Genetic polymorphism in population with diabetic nephropathia: Literature review. *Journal of advances in medicine and medical research*, *29*(9), 1-7.
13. 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.
14. Низамова, Н. Г., Максудова, М. Х., & Жуманазаров, С. Б. (2021). Изучение зависимости приобретенных пороков сердца от степени поражения клапана у пациентов с хронической сердечной недостаточностью. *Моя профессиональная карьера*, *1*(24), 7-19.
15. Шестакова М.В., Шамхалова М.Ш. Диабетическая нефропатия: клиника, диагностика, лечение // Методическое пособие. Москва, 2009г.-29с.

16. Jabbarov, O. O., Tursunova, L. D., Tashpulatova, M. X., Daminov, B. T., Boboev, K. T., & Maksudova, L. I. (2020). Associations of polymorphic markers aluins/deli> D Ace T-786C gene Enos3 in diabetic nefropate progressing for type 2 diabetes mellitus. *International Journal of Research in Pharmaceutical Sciences*, *11*(4), 6028-6032.
17. Munoz J, Lok KH, Gower BA, Fernandez JR, Hunter GR, Lara-Castro C, De Luca M, Garvey WT. Polymorphism in the transcription factor 7-like 2 (TCF7L2) gene is associated with reduced insulin secretion in nondiabetic
women. Diabetes. 2006 Dec;55(12):3630-4.
18. 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.