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Original Article

Analysis and Evaluation of Correlation between DNA Polymorphism in the Genes MTHFR, PAI-1 and Serum Creatinine, Creatinine Clearance and Albumin/Creatinine Ratio in Morning Urine of Patients with Type 2 Diabetes Mellitus and Diabetic Nephropathy

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Abstract

Introduction: Diabetic nephropathy is a major microangiopathic complication of type 2 diabetes and a leading cause of chronic kidney disease (CKD).

Aim: To improve the diagnostic approach to early diagnosis of diabetic nephropathy in patients with type 2 diabetes mellitus.

Materials and methods: One hundred fifty patients were divided into three groups. Group 1 consisted of 67 patients with type 2 diabetes mellitus (DM2) and diabetic nephropathy with stage 1 or 2 of CKD. Group 2 included 45 patients with DM2 without clinical and laboratory evidence for diabetic nephropathy. Group 3 had 38 healthy individuals. The polymorphism of the MTHFR C677T and PAI-14G/5G gene was determined by extracted genomic DNA from peripheral blood cells. All patients underwent a real-time PCR reaction. Serum creatinine, MDRD creatinine clearance, albumin/creatinine ratio were examined.

Results: The correlation analysis we performed showed a very strong correlation of serum creatinine, creatinine clearance and albumin/creatinine ratio with the C677T polymorphism of the MTHFR gene and the 4G/5G polymorphism of the PAI-1 gene. We used descriptive statistics, ANOVA, and multiple comparisons; the level of significance was set at $p<0.05$.

Conclusions: 1. The presence of the T allele in the MTHFR gene determines the tendency to increase serum creatinine, decrease creatinine clearance, and increase the albumin/creatinine ratio in morning urine; 2. The presence of 4G allele in the PAI-1 gene determines the tendency to increase serum creatinine, decrease creatinine clearance, and increase the albumin/creatinine ratio in morning urine.

Keywords

creatinine clearance and albumin/creatinine ratio, diabetic nephropathy, polymorphism C677T MTHFR, polymorphism 4G/5G for PAI-1, serum creatinine

INTRODUCTION

Diabetic nephropathy (DN) is the main microangiopathic complication of type 2 diabetes mellitus (DM2). It is a leading cause of chronic kidney disease (CKD) and kidney failure. Diabetic patients are between 25 and 45 percent of all dialysis patients in both Bulgaria and Europe. The group of diabetics who need dialysis is the biggest of all. Many studies mention the use of different biomarkers preceding the development of CKD. Such biomarkers are: biomarkers for genetic, serum, tubular vascular-endothelial dysfunctions.[1-5]

Methylenetetrahydrofolate reductase (MTHFR) is an enzyme which catalyzes the conversion to 5-methyltetrahydrofolate cosubstrate for homocysteine remethylation to methionine.[6]

MTHFR gene is located in the 1p 36.3 chromosome. Gene polymorphism of MTHFR, C677T (rs1801133), *C*→T transition at nucleotide 677 in exon 4 is a common gene variant of MTHFR. The most common variations of the polymorphism of MTHFR gene are MTHFR C677C = normal MTHFR gene, MTHFR C677T = heterozygous mutation, MTHFR T677T = homozygous mutation. These genetic polymorphisms can play the role of 'defects' which limit the production of the MTHFR enzyme. This mutation causes the amino acid alanine to change into valine. The result is a thermolabile variant of MTHFR with reduced catalytic activity, which can be stabilized by folic acid. The MTHFR T677T homozygous mutations reduce enzyme activity by 50% and are the most common cause of familial moderate hyperhomocysteinemia. This polymorphism determines the catalytic domain of the enzyme and the formation of thermolabile protein. Homocysteine plays a key role in the metabolism of essential amino acids and methionine. Elevated homocysteine levels are identified as a risk factor for DN in DM2. According to Moczulski et al., C677T polymorphism is a risk factor for DN in men with DM2. They have registered high rate of CT and TT genotypes in men on hemodialysis with DM2 which is in correlation with the presence of C677T allele and the development of DN according to studies conducted by Japanese researchers.[7]

Chen et al.[8], summarizing several meta-analyses based on 13 studies containing 891 healthy people (894 with diabetic nephropathy and 1261 with diabetes mellitus and without DN), assess the association between MTHFR C677T polymorphism and type 2 diabetes mellitus and/or diabetic nephropathy. They found that the 667T allele exhibits significant relation with diabetic nephropathy ($p<0.00001$), but there is no relation with diabetes mellitus ($p=0.25$). Movva et al. confirm that MTHFR 677T may be a risk factor for development of diabetic nephropathy.[9] Benrahma et al. have demonstrated that the MTHFR 677T polymorphism may be a risk factor for diabetic nephropathy.[10] Carriers of MTHFR 677T allele are related by a progression of diabetic nephropathy within a period of 5 to 10 years.

Plasminogen activator inhibitor1 (PAI1) is the main inhibitor of fibrinolysis. It is a linear glycoprotein with molecular mass of 48 kDa, which contains 379 amino acids. PAI1 is one of the inhibitors of serine proteinase and is a key regulatory element in fibrinolysis. The main function of PAI1 is to inhibit the activity of the tissue plasminogen activator, which participates in the transformation of plasminogen into plasmin. The increased activity of plasma PAI1 leads to reduced fibrinolytic activity.[11]

The gene encoding PAI1 is located on the short arm of chromosome 7q 21.3 and contains 9 exons and 8 introns. A polymorphism in the promoter region of PAI1 in the base of 675 from the beginning of the transcription region which refers to 3 or 4 guanine bases (4G/5G). 4G/5G polymorphism has a functional role in determining the base levels of PAI1. Homozygous 4G/4G is related to the transcription of the gene and increased gene expression, which leads to a 25% increase in PAI1 plasma concentration in comparison to 5G/5G genotype. Guanine insertion/deletion polymorphism (4G/5G) in the promoter region of the gene on position 675 regulates PAI1 expression and influences the binding of specific transcription factors and gene transcription rate.

Meigs et al. found that increased plasminogen activator inhibitor-1 plasma levels increase the risk for type 2 diabetes.[12] PAI1 4G/5G polymorphism is a main genetic determinant of PAI1 plasma levels, 4G/4G homozygotes increase PAI1 level in comparison to 5G allele carriers. These observations suggest the hypothesis that PAI1 4G/5G polymorphism may be a genetic risk factor for diabetes and diabetic nephropathy. Several studies from 2006 and 2012 found that 4G/4G polymorphism of plasminogen activator inhibitor 1 gene polymorphism increases the risk for developing diabetic nephropathy in patients with type 2 diabetes mellitus.[12-15]

AIM

The object of interest is diabetic nephropathy in patients with DM2.

MATERIALS AND METHODS

One hundred fifty patients were studied and allocated to three groups. Group 1 consisted of 67 patients with DM2 and DN with stage 1 or 2 CKD (serum creatinine 96.22±18.61 μmol/l, creatinine clearance by MDRD 103.26±16.12 ml/min). Group 2 included 45 patients with DM2 and no clinical and laboratory evidence of DN. Group 3 was the control group and consisted of 38 healthy individuals. Diagnosis of DM2 was based on the WHO criteria.

Inclusion criteria for the first two groups

1. Type 2 diabetes mellitus; 2. Age at the debut of diabetes >18; 3. Duration of DM2 more than 3 years; 4. Glycated hemoglobin (HbA1c) up to 7.0%; 5. No infection for the past three months; 6. Normal or medically controlled blood pressure.

Exclusion criteria for the first two groups

1. Type 1 diabetes mellitus; 2. Type 2 diabetes mellitus with poor metabolic control; 3. High grade proteinuria (>3.0 g/l); 4. Primary kidney disease; 5. Glomerulopathy in lupus or other collagenoses; 6. Primary or secondary amyloidosis; 7. Uncontrolled hypertension; 8. Ischemic heart disease and its complications; 9. Vascular brain disease and its complications; 10. Other macroangiopathic complications of diabetes mellitus; 11. COPD, asthma; 12. Chronic liver disease; 13. Neoplastic processes; 14. Acute or chronic inflammation on active treatment; 15. Chronic alcohol abuse; 16. Continuous use (in the last six months and during the study) of nonsteroidal anti-inflammatory drugs, corticosteroids, hormonal drugs, and antioxidants.

Clinical examination

Clinical examination included history, physical examination, as well as laboratory blood tests for glucose levels, creatinine, urea and urine for sediment, ECG, and conventional abdominal echography. At the visit, the diagnosis of diabetes mellitus is confirmed and primary kidney disease is excluded, IHD, CVD, COPD, neoplastic disease, chronic alcohol abuse.

Laboratory tests

Laboratory tests were performed at the central clinical laboratory of St George University Hospital – SOJSC, Plovdiv. The tests included serum creatinine, creatinine clearance by MDRD, and albumin/creatinine ratio **(Table 1)**.

Molecular-genetic analysis

Patients had a genome DNA extraction of peripheral blood cells with the use of DNA isolating kit (QIAamp DNA Mini Kit). All patients had a real-time PCR done with the use of Montania 4896 (Anatolia Geneworks). The kits used for real-time PCR were produced by Generi Biotech and were intended for clinical in vitro diagnosis. The following genes were analyzed for the presence of mutation by allelic discrimination: methylenetetrahydrofolate reductase (MTHFR) for discovering mutation C677T; plasminogen activator inhibitor 1 (PAI1) for mutation 4G/5G.

All kits contained standards for the three genotypes (wild, mutant, and heterozygous) with and included negative control. Amplification conditions for the PCR apparatus followed the manufacturer's recommendations. The process begins with an initial activation of 3 min at 95°C, followed by 50 cycles of 10 seconds denaturation (95°C), 20 seconds annealing+extension (60°C) and end with a final cooling of up to 4°C.

Statistical analysis

The statistical analysis, interpretation, and presentation of the results were performed using SPSS (SPSS Inc., IBM SPSS Statistics) version 21.0 and Microsoft Office Excel 2010. To confirm the hypotheses, the level of significance at which the null hypothesis is rejected was set at $p \leq 0.05$.

The following methods were used: Student's test (independent samples t-test); Fisher's exact test; ANOVA; Chi-squared test; correlation and regression analyses.

RESULTS

The distribution of the three groups is presented in **Table 2**. The groups differed in both age and sex. The controls were the youngest, and there was a difference in the mean age between groups 1 and 2. The distribution by sex was similar – the second group was equal to M/F, in group 1 there were more men, and in the control group there were more women **(Table 2)**.

The results for real-time PCR for determining polymorphism C677T of the gene for MTHFR are presented in **Table 3**. Patients with DM2 and DN with stage 1 and 2 of CKD with a normal genotype were 31.34%, heterozygous C677T – 47.76%, and homozygous 677T>T – 20.90%.

Table 1. Visits and laboratory tests performed

Laboratory test	1 month	6 months	12 months	18 months	24 months
Creatinine	X	X	X	X	X
Creatinine clearance by MDRD	X	X	X	X	X
Albumin/creatinine ratio in morning urine	X	X	X	X	X

Table 2. Distribution of studies patient by group, gender and age

Group	n (%)	Age (mean±SD)	Sex n (%)	
			Women	Men
DM2 and DN with CKD I-II stage	67 (44.67)	60.14±10.96	24 (35.82)	43 (64.18)
DM2 without DN	45 (30.00)	58.49±13.16	22 (48.89)	23 (51.11)
Controls	38 (25.33)	45.80±9.47	32 (84.21)	26 (15.79)
Total	150		78	72

Table 3. Polymorphism C677T of the gene for MTHFR

Group	Total number	Normal genotype MTHFR C677C n (%)	Heterozygous MTHFR C677T n (%)	Homozygous MTHFR T677T n (%)
DM2 and DN with stage 1,2 of CKD	67	21 (31.34%)	32 (47.76%)	14 (20.90%)
DM2 without DN	45	21 (46.66%)	20 (44.44%)	4 (8.90%)
Controls	38	30 (79.00%)	5 (13.00%)	3 (8.00%)

Patients with DM2 and no DN with a normal genotype were 46.66%, heterozygous C677T – 44.44%, and homozygous 677T>T – 8.90%. Healthy controls with a normal genotype were 79.0%, heterozygous – C677T were 13.0%, and homozygous 677T>T – 8.0%. (chi-square 23.94, $p<0.001$) **(Table 3)**.

Furthermore, we have studied the 24-month tendency of the serum creatinine in association with the polymorphism C677T of the gene for MTHFR in patients with DM2 and DN. In homozygous MTHFR 677T>T serum creatinine progressed (117.18–200.13 μmol/l) much faster than the heterozygous MTHFR 677C >T (116.74–176.63 μmol/l) and those with a normal genotype (113.94–157.05 μmol/l) ($p<0.05$) **(Fig. 1)**. The analysis showed a very strong correlation between serum creatinine and the C677T polymorphism of the MTHFR – R2 gene is 0.9989 in homozygotes, R2 – 0.9497 in heterozygotes, and R2 – 0.9988 in those with normal genotype **(Fig. 1)**.

We investigated the 24-month trend of the albumin/creatinine ratio in morning urine in relation with polymorphism C677T of the gene for MTHFR in patients with DM2 and DN. In homozygous MTHFR 677T>T albumin/

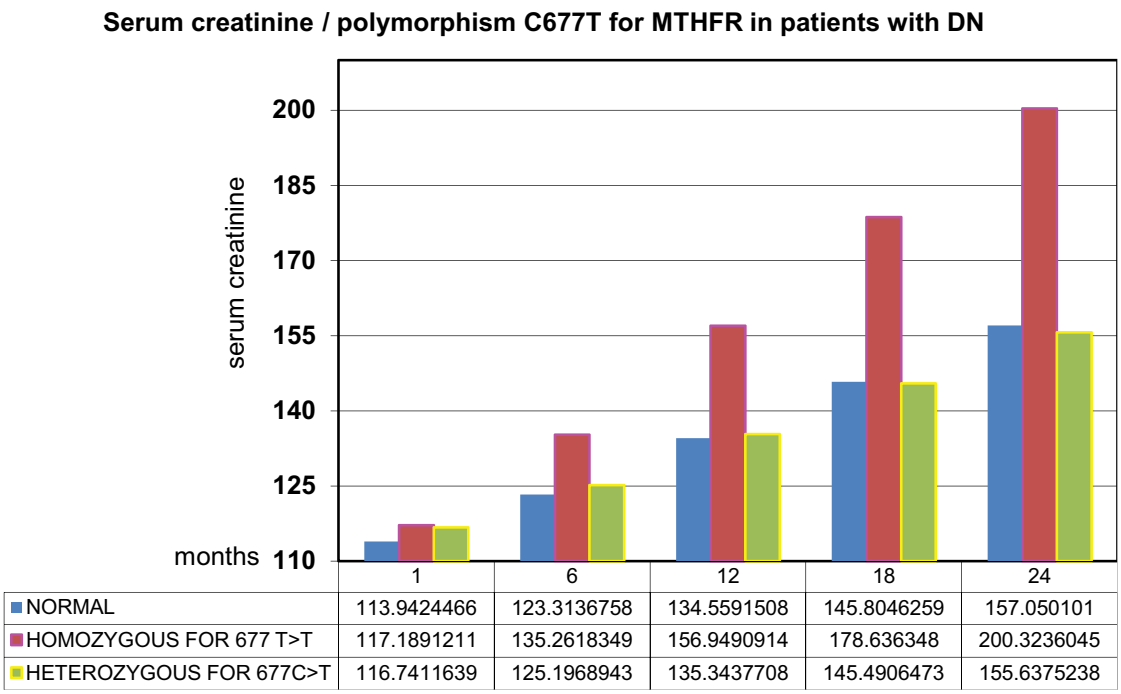
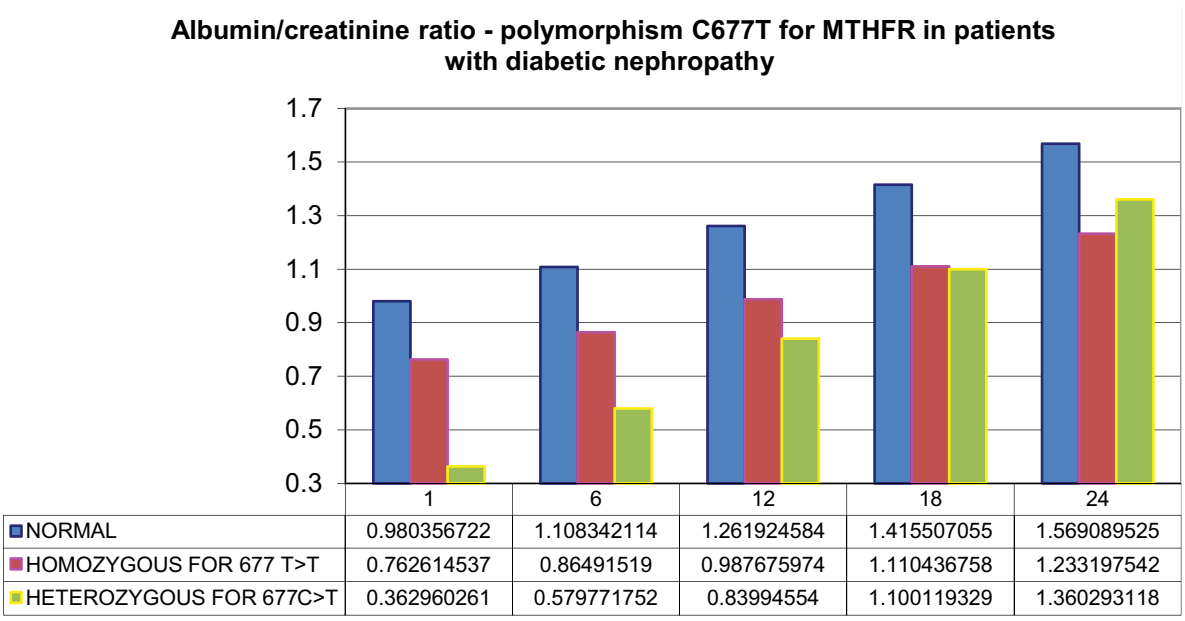


Figure 1. Association between serum creatinine and polymorphism C677T of the gene for MTHFR in patients with DM2 and DN.

creatinine (0.980–1.56 mg/mmol) progressed much faster in comparison to the heterozygous MTHFR 677C >T (0.362–1.360 mg/mmol) and those with a normal genotype (0.762–1.233 mg/mmol). In heterozygous MTHFR 677C >T albumin/creatinine ratio (0.362–1.360 mg/mmol) in morning urine progressed much slower compared to those with a normal genotype (0.762–1.233 mg/mmol) ($p<0.05$) **(Fig. 2)**. The analysis showed a very strong correlation between the albumin/creatinine ratio and the C677T polymorphism of the MTHFR – R2 gene is 0.9412 in homozygotes, R2 – 0.9413 in heterozygotes, and R2 – 0.9988 in those with normal genotype **(Fig. 2)**.

High correlation of creatinine clearance in regard to polymorphism C677T of the MTHFR gene in patients with DM2 and DN is demonstrated – in homozygous MTHFR 677T>T creatinine clearance is the lowest 75.6 ml/min, higher in heterozygous MTHFR 677C>T 108.63 ml/min, and the highest in normal genotype 113 ml/min **(Fig. 3)**. The analysis showed a very strong correlation between creatinine clearance and C677T polymorphism of the MTHFR – R2 gene is 0.8363 ($p<0.05$) **(Fig. 3)**.

The results for the 4G/5G polymorphism of the gene for PAI-1 in patients with DM2 and DN with stage 1 and 2 of CKD are demonstrated – the ones with a normal genotype were 16.4%, heterozygous 4G/5G were 58.2%, and homozygous 4G/4G were 25.4%. Patients with DM2 and no clinical or laboratory evidence of DN with a normal genotype were 55.56%, heterozygous 4G/5G were 40.0%, and homozygous 4G/4G were 4.44%. Healthy individuals with a normal genotype were 71.05%, heterozygous 4G/5G



	1	6	12	18	24
NORMAL	0.980356722	1.108342114	1.261924584	1.415507055	1.569089525
HOMOZYGOUS FOR 677 T>T	0.762614537	0.86491519	0.987675974	1.110436758	1.233197542
HETEROZYGOUS FOR 677C>T	0.362960261	0.579771752	0.83994554	1.100119329	1.360293118

Figure 2. Association between albumin/creatinine ratio and polymorphism C677T of the gene for MTHFR in patients with DM2 and DN.

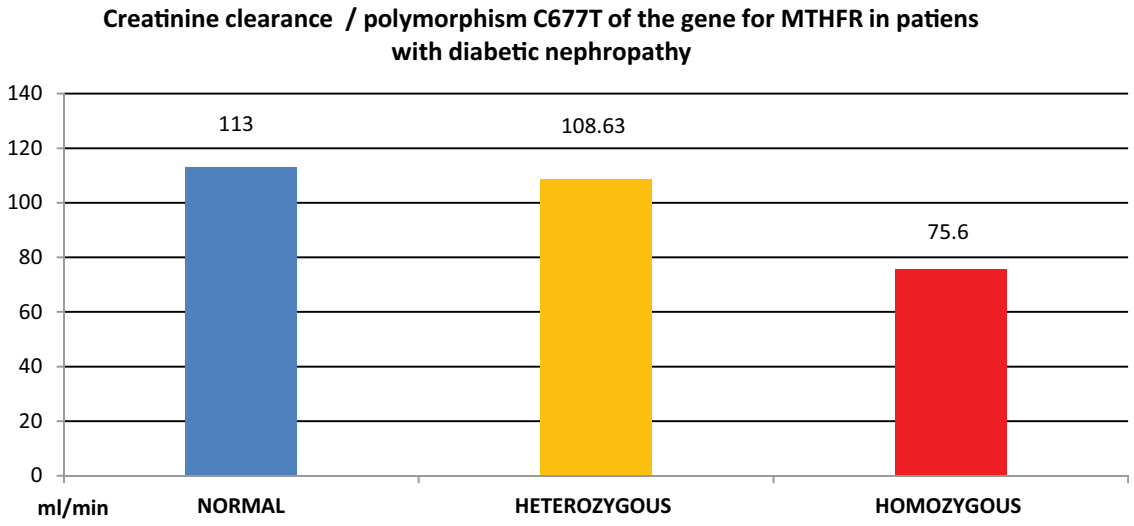


Figure 3. Association between creatinine clearance and polymorphism C677T of the MTHFR - R2 gene.

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– 21.05%, homozygous 4G/4G – 7.9% (chi-square=37.57, p<0.001) **(Table 4)**.

The 24-month tendency of serum creatinine in dependence to 4G/5G polymorphism of the gene for PAI-1 in patients with DM2 and DN was established – in 4G/4G homozygous for PAI-1 serum creatininrison to heterozygous 4G/5G for PAI-1 (118.10–135.74 μmol/l) and those with a normal genotype (101.53–128.86 μmol/l) (p<0.05) **(Fig. 4)**. The analysis showed a very strong correlation between serum creatinine and the 4G/5G polymorphism of the PAI1 – R2 gene is 0.9988 in homozygotes, R2 – 0.9988 in heterozygotes, and R2 – 0.9993 in those with normal genotype **(Fig. 4)**.

We studied the 24-month tendency of albumin/creatinine ratio in morning urine in correlation with polymorphism of the gene for PAI1 in patients with DM2 and DN. In homozygous PAI1 4G/4G albumin/creatinine progressed (0.351–1.514 mg/mmol) much slower in comparison to heterozygous PAI1 4G/5G (0.734–1.384 mg/mmol) and those with a normal genotype (0.727–1.258 mg/mmol). In heterozygous PAI1 4G/5G albumin creatinine ratio (0.734–1.384 mg/mmol) in morning urine progressed much faster in comparison to those with a normal genotype (0.727–1.258 mg/mmol) (p<0.05) **(Fig. 5)**. The analysis showed a very strong correlation between the albumin/creatinine ratio and the 4G/5G polymorphism of the PAI-1 – R2 gene is 0.9988 in homozygotes, R2 – 0.9988 in heterozygotes, and R2 – 0.9988 in those with normal genotype **(Fig. 5)**.

The following results demonstrate the correlation of creatinine clearance and 4G/5G polymorphism of the gene for PAI1 in patients with DM2 and DN at month 6. Creatinine clearance in homozygous 4G/4G for PAI1 4 was the lowest 88.8 ml/min, higher in heterozygous PAI1 4G/5G 99.59 ml/min, and the highest in normal genotype 121 ml/min (p<0.05) **(Fig. 6)**. The analysis showed a very strong correlation between creatinine clearance and the 4G/5G polymorphism of the PAI1 – R2 gene was 0.965 **(Fig. 6)**.

DISCUSSION

Our study shows a much higher distribution of the genotype 4G/4G for PAI-1 and MTHFR T677T among patients with DN in comparison to groups with DM2 and no DN, compared by sex and age, with a similar duration of the disease and glycemic control. We studied the effect of the

Table 4. Polymorphism 4G/5G of the gene for PAI-1

Group	n	Normal genotype 5G/5G - PAI-1 n (%)	Heterozygous 5G/4G - PAI-1 n (%)	Homozygous 4G/4G - PAI-1 n (%)
DM2 and DN with stage 1, 2 of CKD	67	11 (16.4%)	39 (58.2%)	17 (25.4%)
DM2 without DN	45	25 (55.56%)	18 (40.0%)	2 (4.44%)
Controls	38	27 (71.05%)	8 (21.05%)	3 (7.9%)

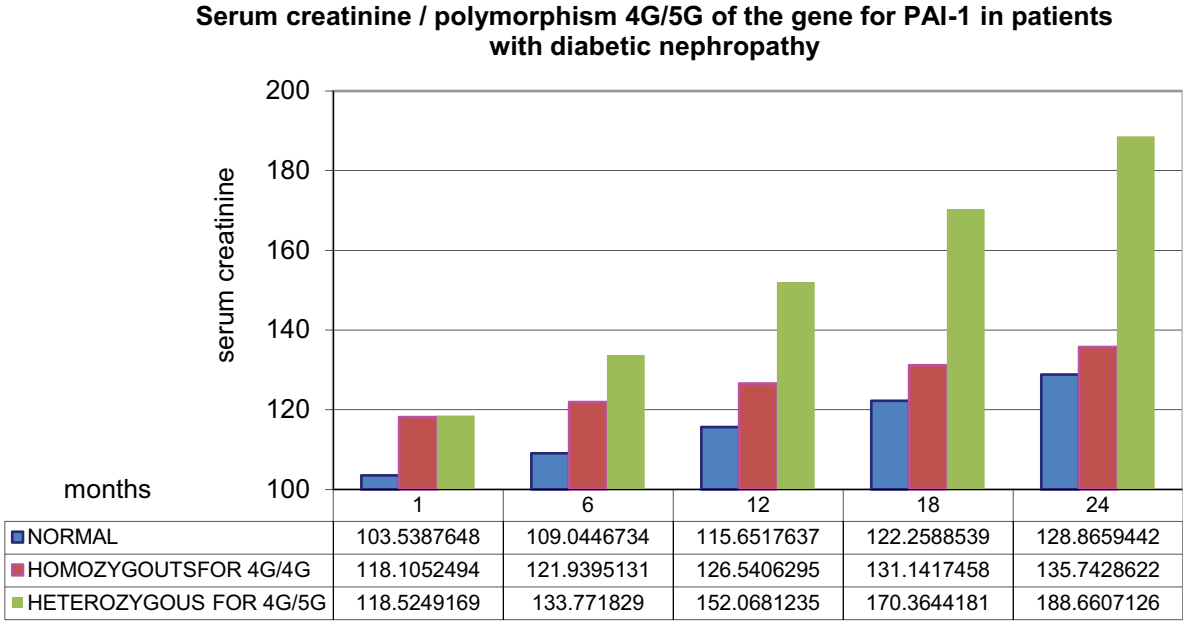

Figure 4. Association between serum creatinine and polymorphism 4G/5G of the gene for PAI-1 in patients with DM2 and DN.

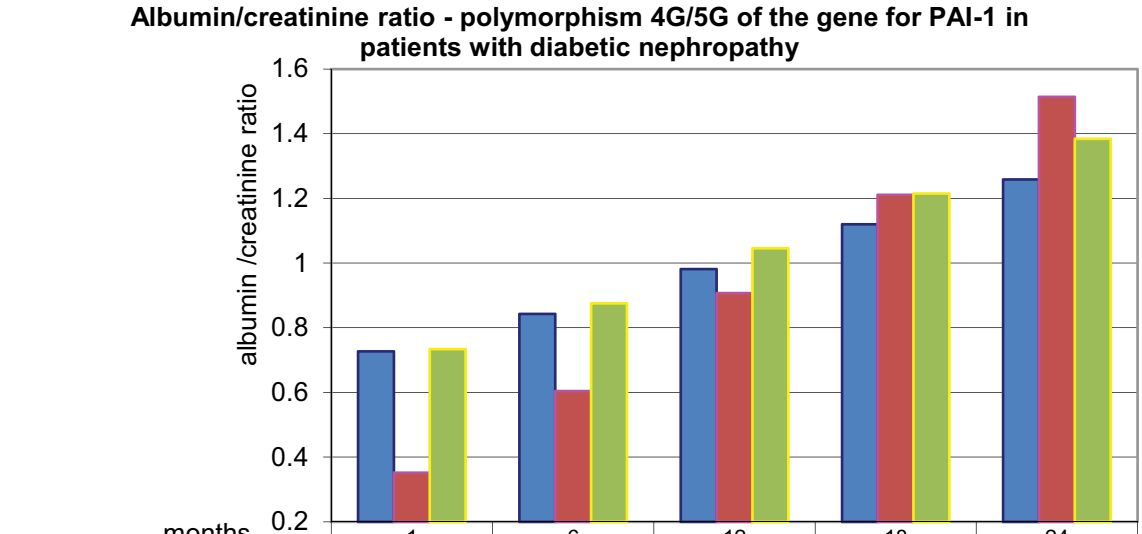

Figure 5. Association between albumin/creatinine ratio and polymorphism 4G/5G of the gene for PAI-1 in patients with DM2 and DN.

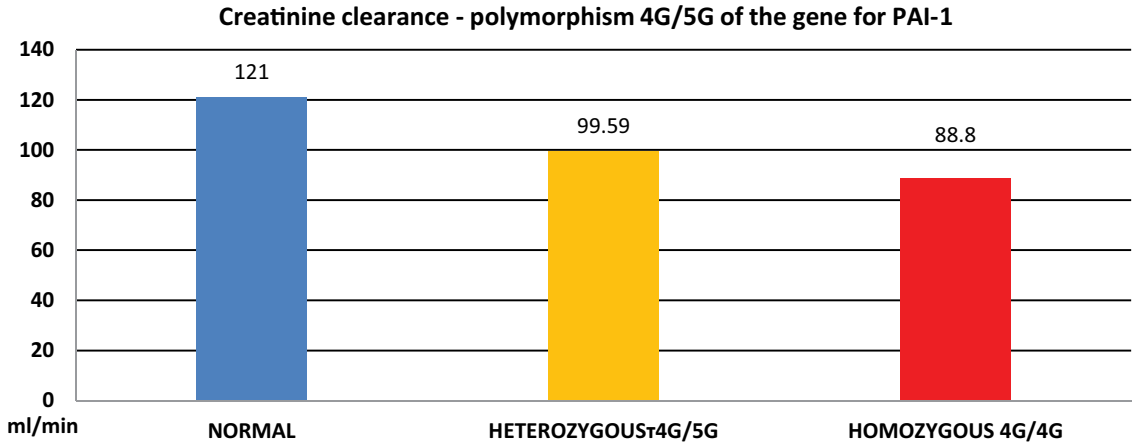

Figure 6. Creatinine clearance and polymorphism 4G/5G of the gene for PAI-1 in patients with DM2 and DN at 6 months.

4G/5G genotypes for PAI-1 and C677T for MTHFR on the progression of DN regarding renal function with the use of serum creatinine, creatinine clearance and albumin/creatinine ratio. The genotype PAI-1 4G/5G and MTHFR C677T are independent risk factors for the development of nephropathy in patients with DM2; they have direct correlation with the progression of CKD. 4G/5G polymorphism for PAI-1 and C677T for MTHFR can be used for an early prognostic marker for the development of diabetic nephropathy and CKD in patients with DM2. Our results correspond to the results reported by Chen et al.[8] summarized in several meta-analyses based on 13 studies with 891 healthy people, 894 with diabetic nephropathy and 1261 with diabetes mellitus without diabetic nephropathy. We found that C677T mutation of MTHFR gene predisposes patients with type 2 diabetes to developing diabetic nephropathy. The T allele of this mutation is related to the more rapid progression of nephropathy to a final stage of kidney failure. Several studies from 2006 and 2020 demonstrated that the 4G/4G polymorphism of the plasminogen activator inhibitor type 1 gene increases the risk for developing diabetic nephropathy in patients with type 2 diabetes mellitus. This polymorphism is related to rapid progression of nephropathy to a final stage of kidney failure, which is fully consistent with our results.[11-14]

CONCLUSIONS

C677T polymorphism of the MTHFR gene is associated with the increase of serum creatinine levels. The presence of a T allele in the MTHFR gene determines the tendencies for increasing serum creatinine, lowering creatinine clearance and increasing albumin/creatinine ratio in morning urine. The 4G/5G polymorphism of PAI1 gene is associated with an increase in serum creatinine. The presence of a 4G allele in the PAI1 gene determines the tendencies for increasing serum creatinine, lowering creatinine clearance, and increasing albumin/creatinine ratio in morning urine.

REFERENCES

1. Paskalev E. Nephrologia. Sofia: Bulgarresurs; 2015: 295-312 [Bulgarian].
2. Tankova C. Diabetes mellitus. Sofia: Paradigma; 2013: 56:300–14. ISBN 978-954-326-201-4 [Bulgarian]
3. Borisova AM, Shinkov A, Vlahov Y, et al. [Prevalence of diabetes mellitus and prediabetes in Bulgaria today]. Endokrinologia 2012; 4:182–92 [Bulgarian].
4. Charakchiev D, Zaharieva S, Angelova G, et al. [Compilation of a national register of patients with diabetes mellitus]. Epidemiologia 2015; (2):19–21 [Bulgarian].
5. Kundurdzhiev A. [Diabetic nephropathy]. Science endokrinologia 2013; 7(6):226–9 [Bulgarian].
6. Li J, Shi M, Zhang H, et al. Relation of homocysteine to early nephropathy in patients with type 2 diabetes. Clin Nephrol 2012; 77(4):305–10.
7. Moczulski D, Fojcik H, Zukowska-Szczechowska E, et al. Effects of the C677T and A1298C polymorphisms of the MTHFR gene on the genetic predisposition for diabetic nephropathy. Nephrol Dial Transplant 2003; 18(8):1535–40.
8. Chen H, Wei F, Wang L, et al. MTHFR gene C677T polymorphism and type 2 diabetic nephropathy in Asian populations: a meta-analysis. Int J Clin Exp Med 2015; 8(3):3662–70.
9. Movva S, Alluri RV, Venkatasubramanian S, et al. Association of methylene tetrahydrofolate reductase C677T genotype with type 2 diabetes mellitus patients with and without renal complications. Genet Test Mol Biomarkers 2011; 15(4):257–61.
10. Benrahma H, Abidi O, Melouk L, et al. Association of the C677T polymorphism in the human methylenetetrahydrofolate reductase (MTHFR) gene with the genetic predisposition for type 2 diabetes mellitus in a Moroccan population. Genet Test Mol Biomarkers 2012; 16(5):383–7.
11. Sprengers D, Kluft C. Plasminogen activator inhibitors. Blood 1987; 69(2):381–7.
12. Meigs B, Dupuis J, Liu C, et al. PAI-1 gene 4G/5G polymorphism and risk of type 2 diabetes in a population-based sample. Obesity 2006; 14(5):753–8.
13. Xu F, Liu H, Sun Y. Association of plasminogen activator inhibitor-1 gene polymorphism and type 2 diabetic nephropathy. Renal Failure 2016; 38(1):157–62.
14. Shirakawa J, Togashi Y, Tajima K, et al. Plasminogen activator inhibitor-1 is associated with renal dysfunction independent of BMI and serum lipid levels in patients with type 2 diabetes. Diabetes Res Clin Pract 2012; 97(1):e9–12.
15. Wong TY, Poon P, Szeto CC, et al. Association of plasminogen activator inhibitor-1 4G/4G genotype and type 2 diabetic nephropathy in Chinese patients. Kidney Int 2000; 57(2):632–8.

Анализ и оценка корреляции между полиморфизмом ДНК в генах MTHFR, PAI-1 и сывороточным креатинином, клиренсом креатинина и соотношением альбумин/креатинин в утренней моче больных сахарным диабетом 2 типа и диабетической нефропатией

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Резюме

Введение: Диабетическая нефропатия является основным микроангиопатическим осложнением сахарного диабета 2 типа и ведущей причиной хронической болезни почек (ХБП).

Цель: Усовершенствовать диагностический подход к ранней диагностике диабетической нефропатии у больных сахарным диабетом 2 типа.

Материалы и методы: Сто пятьдесят пациентов были разделены на три группы. 1-ю группу составили 67 больных сахарным диабетом 2-го типа (СД2) и диабетической нефропатией с 1-й или 2-й стадией ХБП. Во 2-ю группу вошли 45 больных СД2 без клинико-лабораторных признаков диабетической нефропатии. 3-ю группу составили 38 здоровых лиц. Полиморфизм гена MTHFR C677T и PAI-1 4G/5G определяли по выделенной геномной ДНК из клеток периферической крови. Всем пациентам была проведена ПЦР-реакция в реальном времени. Исследовали креатинин сыворотки, клиренс креатинина MDRD, соотношение альбумин/креатинин.

Результаты: Проведённый нами корреляционный анализ показал очень сильную корреляцию сывороточного креатинина, клиренса креатинина и соотношения альбумин/креатинин с полиморфизмом C677T гена MTHFR и полиморфизмом 4G/5G гена PAI-1. Мы использовали описательную статистику, ANOVA и множественные сравнения; уровень значимости был установлен на уровне $p<0.05$.

Заключение: 1. Наличие аллеля T в гене MTHFR определяет тенденцию к повышению уровня креатинина в сыворотке крови, снижению клиренса креатинина и повышению соотношения альбумин/креатинин в утренней моче; 2. Наличие аллеля 4G в гене PAI-1 определяет тенденцию к повышению уровня креатинина в сыворотке крови, снижению клиренса креатинина и повышению соотношения альбумин/креатинин в утренней моче.

Ключевые слова

клиренс креатинина и отношение альбумин/креатинин, диабетическая нефропатия, полиморфизм C677T MTHFR, полиморфизм 4G/5G для PAI-1, креатинин сыворотки