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Study Of Clinical And Laboratory Aspects Of Nephropathy And 1166 A>C Polymorphism Of Agtr1 Gene In Patients With Type 1 Diabetes Mellitus In Uzbek Population

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Key words: type 1 diabetes, diabetic nephropathy, gene AGTR1 1166 A> C

Relevance

Today, diabetes mellitus is one of the most common diseases among children and adolescents, and is considered a non-infectious epidemic of the 21st century. According to the International Diabetes Federation IDF (2017), and to the 8th edition of the IDF Atlas, the total number of patients with type 1 diabetes mellitus under the age of 20 increased to 1 million 106 thousand, 586 thousand of which are children (age <15 years) with a total child population in the world of 1.94 billion. For the period 2000-2016 the prevalence rate of type 1 diabetes mellitus in children from 0 to 14 years was an average of 12.7 per 100 thousand children. Diabetes mellitus remains a global medical and social health problem all over the world. The greatest danger of diabetes mellitus is associated with its vascular complications, in particular, diabetic nephropathy (DN), which develops in 30-40% of patients with type 1 and type 2 diabetes mellitus and occupies a leading position among the causes of End Stage Renal Failure (ESRF) worldwide [4]. ESRF due to diabetic nephropathy remains the main cause of death of patients with type 1 diabetes (T1D), and in patients with type 2 diabetes (T2D) it ranks second after cardiovascular disease.

The cost of providing renal replacement therapy to patients with ESRF as the outcome of diabetic nephropathy, as well as for the treatment of its complications, is constantly growing and a heavy burden falls on health budget in different countries. In many developed countries (USA, Germany, Japan) diabetic nephropathy ranks first in the structure of dialysis services, reaching 35-45% [12]. Diabetic nephropathy, as a form of pathology in diabetes mellitus, is characterized by a complex of lesions of the arteries, arterioles, glomeruli and tubules of the kidneys, resulting from metabolic disorders of carbohydrates and lipids [21, 1]. Today, the term "diabetic nephropathy" is more commonly used, since the term "diabetic

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glomerulosclerosis" reflects already advanced morphological changes. It is customary to distinguish three stages of DN: the stage of microalbuminuria; the stage of proteinuria with preserved renal function and the stage of chronic kidney disease (CKD) [23,24].

Over the past decades, due to the development of new laboratory methods, the possibilities and standards for diagnosing diabetic kidney disease have changed [25]. However, modern screening tests can detect diabetic nephropathy (DN) only on the 1st clinical stage - the stage of microalbuminuria, while skipping the initial structural and functional disorders that develop long before the increase in albumin excretion. The earliest signs of kidney damage can be detected in the first 5 years from the onset of type 1 diabetes mellitus (D1T) [5]. According to some researchers, it is during this period that the beginning of preventive measures against progression of DN can be most effective. Throughout the world, DN and resulting chronic kidney disease (CKD), are the leading causes of death of patients with D1T [5]. The appearance of microalbuminuria already indicates the sclerosis of at least 20-25% of nephrons, and progression to the stage of proteinuria – the loss of 50-70% of glomeruli, which indicates irreversible kidney damage, when the effectiveness of therapy is extremely limited, and progressive decrease in filtration function becomes inevitable [25]. Additionally in recent years, tubulointerstitial disorders, which, according to a number of studies, precede the development of glomerular lesions, have become increasingly important in the pathogenesis of DN [26]. All of the above determines the relevance of the search for early non-invasive markers of preclinical (pre-microalbuminuria) diagnosis of DN. Potential markers of DN development can be divided into several subgroups: 1) markers of tubular damage; 2) products of extracellular matrix metabolism; 3) podocytes and markers of their damage; 4) growth factors and 5) immuno-inflammatory factors. In the pathogenesis of DN, activation of the local renal renin-angiotensin system (RAS) is also of great importance, leading to the development of systemic and intra-glomerular hypertension. Therefore, genes encoding components of RAS: angiotensin-converting enzyme (ACE) gene, angiotensinogen (AGT) gene, endothelial nitric oxide synthase (eNOS3) gene and E-1 (EDN1) gene are of interest as candidate genes for diabetic nephropathy and CKD in type 1 and type 2 diabetes mellitus.

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Objective.

Objective of this research was to study the character of nephropathy course depending on the severity of carbohydrate metabolism disorder and functional activity of the kidneys, and to study the frequency distribution of alleles and genotypes and to identify the correlation between polymorphic markers 1166 A>C in AGTR1 gene in patients with type 1 diabetes mellitus with risk of diabetic nephropathy.

Materials and methods.

We examined 100 patients with type 1 diabetes mellitus, among them 80 patients with normoalbuminuria and 20 patients in the stage of microalbuminuria who were treated at the Republican specialized scientific-practical Center of Endocrinology in the Department of pediatric endocrinology at the age of 1-14 years, with disease duration from 1 to 10 years. Among them, there were 48 boys, and 52 girls. Glycated hemoglobin was determined by photometric method using immunochemical kit. Glomerular filtration rate (GFR) was calculated by the Schwartz formula. The state of kidney function in patients with DN was assessed according to the Stages of Chronic Kidney Disease (CKD) in Recommendations of the National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF/DOQI) [19]. Alleles identification was carried out by polymerase chain reaction (PCR). Genomic DNA was isolated from patients whole blood; standard sets of primers of the company "Litech"-"SNP" (Moscow) were used in the research. Visualization of amplification products was performed by electrophoresis in 3% agarose gel with addition of ethidium bromide in ultraviolet light. The genotype distribution was checked for deviation from the Hardy-Weinberg equilibrium. Differences were considered statistically significant at $p<0.05$.

Table 1. Characteristics of groups of patients with type 1 diabetes mellitus with presence and absence of diabetic nephropathy (DN)

Indicator	DN «-», n = 80	DN «+», n = 20
Age, years	10,45±0,26	11,25± 0,56
Gender, male/female	39/41	7/13
Duration of diabetes, years	4,57±0,50	4,75± 0,60

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Index of Mass Corporal kg/m^2	17,07±0,28	18,4± 1,02
Glycated hemoglobin, %	9,63±0,28	9,90±0,63
TC, mmol/l	3,91±0,07	4,24± 0,14
Triglycerides, µmol/l	0,80±0,04*	2,07± 0,41
Creatinine, µmol/l	67,3±1,44	74,9± 5,53
GFR, ml/min	78,05 ±1,63	72,1 ±3,85

Note. The data is presented in the form of an average value and a standard deviation. Frequency indicators are shown as a percentage of the total number of patients in this group.* P<0.05 reliability of differences between groups of patients with type 1 diabetes with normoalbuminuria and microalbuminuria

Results and discussion.

The examined patients were divided into two groups: 1 – with normoalbuminuria and 2 – with microalbuminuria. Among the examined groups of patients 66.6% were girls and 33.4% - boys. In group 1 dibetic neuropathy was in 30% of patients, in group 2 – in 80%; dibetic retinopathy was not detected in group 1, in group 2 – in 5% of patients. The analysis of clinical and anamnestic data showed that among examined patients heredity for diabetes mellitus was in 42.5%, specifically in the group with microalbuminuria it was - 50%, in the group with normoalbuminuria - 35%. The duration of diabetes mellitus in group 1 was 3.76±0.22, in group 2 - 4.75±0.56 years. These data indicate that the progression of nephropathy is not always associated with duration of diabetes, most likely it is due to hereditary and genetic factors. Although according to Smirnov I.E., and co-authors (2015) the frequency of diabetic nephropathy detection is closely related to the duration of diabetes mellitus, this correlation is more studied in type 1 diabetes mellitus, due to a more accurate determination of diabetes onset. The frequency of DN development in patients with T1D duration up to 10 years is 5-6%; up to 20 years - 20-25%; up to 30 years – 35-40%; up to 40 years - 45%; the maximum peak of DN development falls on the period from 15 to 20 years of diabetes progress [7,4,24,20]. The formation of kidney lesions due to diabetes mellitus and the development of DN is a continuously progressive multifactorial process, among the pathogenetic theories of which metabolic,

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hemodynamic and genetic theories are recognized as significant [13-11]. In order to study the effect of carbohydrate metabolism on the development of DN in children and adolescents, we studied the level of HbA1c in both groups: all the examined patients were at the stage of decompensation, the level of glycated hemoglobin (HbA1c) was 9.5%, in particular in group 1 - 9.37%, in group 2 - 9.9%; there was no statistically significant difference in the studied groups ($p > 0.05$). Indicators of fasting glycemia, glycemia 2 hours after meal and the average daily glycemia in both groups were: in group 1 - 8.4; 11.9; 9.87; in group 2 - 8.5; 11.7; 10.1 mmol/l. Glomerular filtration rate (GFR) averaged 72.1 ml/min, which corresponds to the second stage of chronic kidney disease. The role of metabolic disorders, mainly hyperglycemia, in the pathogenesis of DN has been conclusively proven by the Diabetes Control and Complications Trial Research Group (DCCT, 2004). The concept "without diabetes there are no diabetic complications" is basic in understanding the nature of diabetic complications, including nephropathy. However, a number of studies have shown that as DN develops, the direct correlation between nephropathy progression and the level of carbohydrate metabolism compensation disappears. It seems that the pathological process in the kidneys acquires an independent significance (F. V. Valeeva, 2005). At the same time, an increasing number of research results show the importance of dyslipidemia in the genesis of diabetic kidney damage already in the early stages of diabetes in children and adolescents [6]. These results correspond to the obtained data on lipid metabolism, in particular, the level of triglycerides in the microalbuminuria group was 2.07 ± 0.41, statistically significantly higher than in the first group in which it was 0.89 ± 0.13 ($p<0.05$).

A significant breakthrough in the diagnosis of the preclinical stage of nephropathy was the adoption of Program of Screening for Diabetic Nephropathy (DN) in the framework of the Saint Vincent Declaration, according to which microalbuminuria is the main laboratory criterion for early stage of DN. When forming a risk group in children and adolescents, a system of accounting for standard risk factors is used, the role of which is convincingly proven in multicenter studies, the main contingent of which is adult patients with diabetes mellitus (K. Raile et al., 2007). At the same time, the clinical and epidemiological aspects and risk factors in children and adolescents with diabetes mellitus, predisposing to the development of

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nephropathy, are poorly studied.

When studying the diagnostic criteria of the early stages of DN, the main attention of researchers is drawn to the state of the glomerular apparatus. The role of hyperfiltration as an early diagnostic indicator of DN is discussed. The appearance of protein in the urine, albumin in particular, is one of the important diagnostic signs of kidney pathology, nevertheless, a number of facts indicate the possibility of the appearance of albuminuria in some physiological conditions. In this regard, the issue of the role of transient microalbuminuria as a potential risk factor for the development of DN in patients with type 1 diabetes in childhood and adolescence remains unresolved. The assessment of the functional state of the medulla of kidney structures and determination of its concentration ability remains an urgent task in diabetology. The multifactorial genesis of nephropathy in type 1 diabetes determines the need to study the role of genetically determined factors in the development of disease complications. It should be noted that to date, the "main" gene for predisposition to diabetic nephropathy has not been found (S. Maeda, 2008). It has been established that the basis for the prevention and treatment of DN is the achievement and maintenance of stable metabolic compensation of disorders of not only carbohydrate, but also lipid metabolism. The optimal insulin therapy adjustment remains the main task in complications prevention in type 1 diabetes, as evidenced by the results of prospective studies of DCCT. The main method of pathogenetic therapy of DN is prescription of drugs from the group of angiotensin converting enzyme (ACE) inhibitors. Studies have shown the high effectiveness of this group of drugs in the treatment of nephropathy in type 1 diabetes, including early stages of DN [22]. However, even with the timely, regular use of ACE inhibitors, it is not always possible to achieve effective control of the progression of nephropathy. In this regard, the search for new ways to increase the effectiveness of pathogenetic therapy of DN is becoming relevant. Our analysis of the obtained data on clinical, anamnestic, biochemical indicators showed that carbohydrate and lipid metabolism is not always associated with the severity of DN, duration of diabetes mellitus, and glycemia rate.

Widely distributed among various tissues, the AGTR1 gene provides numerous vital biological effects, such as contraction of vascular smooth muscles, stimulation of proliferation and thickening of vascular smooth

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muscles, and acceleration of aldosterone secretion, which are associated with maintaining blood pressure and target organs damage. As a G-protein coupled receptor, AGTR1 has 7 highly conserved transmembrane functional domains. After binding to angiotensin, AGTR1 can activate protein G and 2 intracellular signaling pathways via inositol triphosphate and acetoglyceride. In one pathway, calcium release activates protein kinases to stimulate protein synthesis; while in the other pathway, cascade amplification of protein kinases activates MAPK, which can stimulate the expression of many proto-oncogenes after penetration into the nucleus and thus further accelerate cell division and proliferation. 5 polymorphisms have been identified in the AGTR1 gene, namely A1166C, T573C, A1062G, G1517T and A1878G, of which the first three are more common. A1166C polymorphism is located in the 3'-untranslated region of the gene, which theoretically does not affect the open reading frame and the coding process of the AGTR1 protein. But if it has a disequilibrium linkage with adjacent chromosome positions with functional abnormalities, a number of actions can occur in the stability of AGTR1 gene mRNA expression, quantity and distribution density of AGTR1, as well as the affinity of AGTR1 for angiotensin II, which enhances the reactivity of angiotensin II and induces the onset and development of diabetic nephropathy [16.2].

Accumulating studies have discussed predisposition to DN in light of A1166C polymorphism, but no consensus has been reached so far. For example, Doria et al. [8] and Gallego et al. [15] insisted that there was no significant correlation between A1166C polymorphism of AGTR1 gene and the risk of DN in Caucasian populations. However, a study by Shah et al. [27], revealed a significantly higher frequency of the C-allele of AGTR1 A1166C polymorphism in patients with DN in Indian population, demonstrating the close correlation between polymorphism and disease in studied population. In addition, Yin et al. [28] in their studies in China also found that the C-allele of polymorphism is much more common in the DN group than in healthy control group and in diabetes group without nephropathy. All discrepancies between the above data can be partially explained by the different genetic backgrounds of the participants in these studies, different criteria for selecting samples for the study, and uneven sample size. System analysis urgently needed to solve these problems.

In order to obtain a reliable result on the genetic correlation between

AGTR1 A1166C polymorphism and the risk of DN, this meta-analysis was carried out in accordance with the PRISMA guidelines. After statistical analysis, the results showed that AGTR1 A1166C polymorphism had a significantly increasing effect on DN predisposition in the general analysis, and a similar correlation was also found in Asian and D2T groups after analysis of subgroups by ethnicity and type of diabetes. However, no significant correlation was observed in the Caucasian population and the D1T group. The results partially corresponded to the results of a similar meta-analysis performed by Ding et al. [9]. Their combined analysis showed that AGTR1 A1166C polymorphism was obviously associated with DN in patients with type 2 diabetes. Moreover, the significant correlation did not change after stratification analysis by ethnic background.

For most polymorphic markers of the angiotensin II type 1 receptor gene (AT2RI), no association with DN was found in type 1 diabetes [18,10,3]. Only in the case of polymorphic marker A1166 of AT2R1 gene in homozygous carriers of the C-allele, with consistently high hyperglycemia in the first 10 years of diabetes, the relative risk of developing DN was significantly higher than in patients with AA genotype [17]. Our comparative analysis of the distribution of allele frequencies and genotypes of AGTR1 polymorphism did not reveal significant differences in patients without DN in the studied population (Table 2). As mentioned above, the literature data on this issue is contradictory and probably depends on the ethnic characteristics of the sample. However, according to our study, the ratio of CC and AC pathological genotypes in the second group of patients with diabetic nephropathy was significantly higher than in the control group (Table 3), which suggests the involvement of AGTR1 polymorphism in the development of DN in patients with type 1 diabetes.

Table 2. Comparative analysis of frequency distribution (%) of alleles and genotypes of AGTR1 gene in patients with type 1 diabetes mellitus without diabetic nephropathy

Alleles	**Cases**	**Controls**	χ^2	***p***	***OR***	
	n = 77	n = 94			Val.	95% CI
Allele *A*	0.851	0.910	2.85	0.09	0.57	0.29 – 1.10

Allele *C*	0.149	0.090			1.77	0.91 – 3.44

Genotypes	**Cases**	**Controls**	χ^2	***p***	***OR***	
	n = 77	n = 94			Val.	95% CI
Genotype *A/A*	0.727	0.830	2.75	0.25	0.55	0.26 – 1.14
Genotype *A/C*	0.247	0.160			1.73	0.81 – 3.68
Genotype *C/C*	0.026	0.011			2.48	0.22 – 27.88

Hardy-Weinberg equilibrium for cases (χ^2 test, df = 1)

Genotypes	**Cases**	**HWE**	χ^2	***p***
	n = 77			
Genotype *A/A*	0.727	0.724	0.06	0.8
Genotype *A/C*	0.247	0.254		
Genotype *C/C*	0.026	0.022		

Table 3. Comparative analysis of frequency distribution (%) of alleles and genotypes of AGTR1 gene in patients with type 1 diabetes mellitus with diabetic nephropathy

Genotypes	**Cases**	**Controls**	χ^2	***p***	**OR**	
	n = 20	n = 94			Val.	95% CI
Genotype *A/A+A/C*	0.900	0.989 ***OR***	5.14	0.02	0.10	0.01 – 1.12
Genotype *C/C*	0.100	0.011			10.33	0.89 – 120.10

Hardy-Weinberg equilibrium for cases (χ^2 test, df = 1)

Genotypes	**Cases**	**HWE**	χ^2	***p***
	n = 20			
Genotype *A/A*	0.750	0.681	4.62	0.03

Genotype *A/C*	0.150	0.289		
Genotype *C/C*	0.100	0.031		

Summary

1. The analysis of clinical and anamnestic data showed that among examined patients heredity for diabetes mellitus was in 42.5%, specifically in the group with microalbuminuria it was - 50%, in the group with normoalbuminuria - 35%. The duration of diabetes mellitus in group 1 was 4,57±0,50, in group 2 - 4,75±0,60 years. These data indicate that the progression of nephropathy is not always associated with duration of diabetes, most likely it is due to hereditary and genetic factors.
2. The level of glycated hemoglobin (HbA1c) was 9.5%, in particular in group 1 - 9.37%, in group 2 - 9.9%; there was no statistically significant difference in the studied groups ($p > 0.05$). Indicators of fasting glycemia, glycemia 2 hours after meal and the average daily glycemia in both groups were: in group 1 - 8.4; 11.9; 9.87; in group 2 - 8.5; 11.7; 10.1 mmol/l. The results showed that there was no correlation between the progression of nephropathy and the level of compensation of carbohydrate metabolism.
3. Indicators of lipid metabolism, in particular the level of triglycerides in the group with microalbuminuria was significantly higher than in the first group and amounted to 2.07±0.41, compared to the group with normoalbuminuria - 0.89±0.13 ($p<0.05$).
4. Distribution of alleles frequencies and genotypes of AT2R1 gene polymorphism did not reveal significant differences in patients without diabetic nephropathy in the examined population. In patients of group 2 with diabetic nephropathy, the ratio of pathological CC and AC genotypes was significantly higher than in control group, which suggests the correlation between of AGTR1 gene polymorphism and development of diabetic nephropathy in patients with type 1 diabetes.

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Resume:
Diabetes mellitus remains a global medical and social health problem all over the world. The greatest danger of diabetes mellitus is associated with its vascular complications, in particular, with diabetic nephropathy, which develops in 30-40% of patients with type 1 and type 2 diabetes and occupies a leading position among the causes of End Stage Renal Failure worldwide. Indicators of lipid metabolism, in particular the level of triglycerides in the group with microalbuminuria was significantly higher than in the first group. The results of the study showed that there was no correlation between the progression of nephropathy and the level of compensation of carbohydrate metabolism. Also in this study, for the first time, the frequency distribution of alleles and genotypes of AGTR1 gene was studied, and the association of polymorphic markers 1166 A>C in AGTR1 gene in patients with type 1 diabetes in Uzbek population was revealed.