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Genetic Determinism Of Chronic Kidney Disease By Ace Gene In Children And Adolescents Of The Uzbek Population With Type 1 Diabetes According To The K/Doqi Recommendation (2012)

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ABSTRACT

The study aimed to assess the functional state of the kidneys and to study the relationship of I/D polymorphism of the ACE gene with the stage of chronic kidney disease in children and adolescents of the Uzbek population with type 1 diabetes according to the new recommendations of K/DOQI (2012). We examined 120 children and adolescents with type 1 diabetes. Clinical, biochemical and genetic studies have been carried out. The study revealed that children with diabetes in the stage of compensation (HbA1c ≤7.5%) have CKD stages II (28.6%) and III (4.8%). The use of the new classification K/DOQI (2012) reveals a decrease in kidney function at earlier stages, in 61.9% of children and adolescents with type 1 diabetes, even at the NAU stage, a GFR of 80.6 ± 7.5 ml/min/1.73m^2, which corresponds to stage II of CKD and 16.7% have a GFR of 45.1 ± 9.5 ml/min/1.73m^2, which corresponds to stage III of CKD. Also, 28.6% of children and adolescents at the MAU stage have CKD II, 75.0% of CKD stage III, respectively. ACE I/D polymorphism is a molecular genetic marker of susceptibility to the development of CKD type 1 diabetes in children and adolescents.

KEYWORDS

Diabetes mellitus, children, adolescents, CKD, ACE gene polymorphism.

INTRODUCTION

Diabetes mellitus (DM) and its complications, which continue to increase every year, cause great human suffering and huge economic costs. Chronic complications of the disease are increasing proportionally to the increase in the incidence of diabetes. Every year 5.5% of

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patients with diabetes mellitus die from complications, and the mortality rate among this category of patients is 2–4 times higher than among those without disorders of carbohydrate metabolism. Type 1 diabetes mellitus (type 1 diabetes) is one of the most severe endocrine diseases in children and adolescents. The dramatic nature of the problem of type 1 diabetes in the population of children and adolescents is determined by a pronounced violation of the child's quality of life, early development of complications with disability of patients and a decrease in life expectancy [Surikova SV, 2008; Panfilova V.N., 2010].

The main threat is posed by late complications of diabetes, in particular diabetic nephropathy (DN). DN develops mainly after 5-10 years from the onset of the disease and quickly enough leads to chronic renal failure (CRF) - every fourth to the fifth patient with type 1 diabetes dies from chronic renal failure [Shestakova MV, Dedov II. 2009; Kuraeva T.L., 2003].

According to the screening data carried out in Uzbekistan in 2012, the prevalence of DN 4-5 degrees was 4.8% among children and 10.8% among adolescents with type 1 diabetes. [Rakhimova G.N., Alimova N.U., 2015]. To work out the optimal strategy for the management of patients with progressive decline in renal function, uniform definitions and classification were required, agreed throughout the nephrological world. This was facilitated by the creation in 2002, with revision in 2012 as part of the development of the Kidney Disease Outcomes Quality Initiative (KDOQI), of the US National Renal Fund guidelines, the first part of which contained the definition and division of the new stage. the supranosological concept of "chronic kidney disease" (CKD) [A. Zemchenkov, 2007; KDOQI, 2012; Coresh J. 2007; Levey A., 2007].

The term CKD in paediatrics was first used by R.J. Hogg in 2003, the definition and classification of this condition by stages in children do not differ from those in adults [Hogg R., 2003]. The K/DOQI guidelines define CKD, regardless of the patient's age, as the presence of kidney damage for 3 months or more, characterized by structural or functional renal impairment with or without a decrease in the glomerular filtration rate (GFR) [KDOQI, 2012].

One of the leading directions in the development of nephrology is the molecular genetic study of endogenous/genetic factors leading to the disease. To study the role of hereditary factors in the development of diseases, the definition of polymorphic markers of candidate genes is used. As candidate genes, products, the expression of which can determine the rate of progression of renal failure, are primarily considered genes encoding components of the renin-angiotensin-aldosterone system [Kaliev RR, 2005; Zyablitsev S.V., 2012; Vikulova O.K., 2003.]. It is important to study the clinical and genetic characteristics of CKD in order to understand the pathogenetic mechanisms of the formation of nephrosclerosis and improve preventive measures. The study of polymorphic markers of genes encoding regulatory proteins and receptors of the renin-angiotensin system makes it possible to identify groups of patients with an increased risk of developing the progression of the pathological process, microvascular complications. Genetic research can be the basis for personalizing kidney disease.

In the literature for the last 5-10 years, there are no data on the assessment of GFR depending on the I/D polymorphism of the ACE gene in diabetes mellitus. For the first time in children and adolescents with type 1 diabetes of the Uzbek population, the

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relationship of I/D polymorphism of the ACE gene with the stage of chronic kidney disease will be studied according to the new recommendations of K/DOQI (2012).

PURPOSE OF THE STUDY

To assess the functional state of the kidneys and to study the relationship of I/D polymorphism of the ACE gene with the stage of chronic kidney disease in children and adolescents of the Uzbek population with type 1 diabetes according to the new recommendations of K/DOQI (2012).

MATERIALS AND METHODS

120 children and adolescents with type 1 diabetes were examined, including 53 males (44.2%) and 67 females (55.8%). The average age of the patients was 13.8 ± 2.7 years (Me 15.0; IQR 13.0-16.0).

For rapid assessment and monitoring of renal function, the GFR value was assessed, which rather informatively reflects the state of the kidneys. There is a close relationship between the level of GFR and the presence of certain manifestations or complications of CKD. All children were calculated GFR (eGFR) according to the Schwartz formula, taking into account gender and age: GFR = [0.0484*height (cm)]/blood creatinine (μmol/l), the data obtained were standardized on the body surface. [Ivanova I.E., 2011].

Stages of chronic kidney disease were classified in accordance with the recommendations of K/DOQI (2012) by GFR: Stage I - GFR ≥ 90ml/min/1.73m2, II - GFR 89-60 ml/min/1.73m2, III - GFR 59 -30 ml/min/1.73m2, IV - GFR 29-15 ml/min/1.73m2, V - GFR 15 or less ml/min/1.73m2.

Isolation of genomic DNA and genotyping by I/D polymorphic marker of the ACE gene (carried out in the Laboratory of Functional Human Genomics of the Institute of Genetics and Experimental Biology of Plants of the Academy of Sciences of the Republic of Uzbekistan). DNA isolation was performed according to Higuchi H. Erlich (1989) using a dry Diatom ™ DNA Prep 200 reagent kit.

The results were statistically processed using the STATISTICA 6 and Biostat programs. Odds ratio (OR) and 95% confidence interval (95% CI) were calculated using logistic regression. The significance of differences in indicators was assessed using the nonparametric $\chi 2$ test (Pearson's test). Quantitative indicators are presented as M ± SD, as well as median (Me) and 25 and 75 percentiles (IQR). Differences between groups were considered statistically significant at $p = 0.05$.

RESULTS

According to the concept of CKD, the stage of renal pathology is assessed by the value of GFR, which is recognized as the most fully reflecting the number and total volume of nephrons' work, including those associated with the performance of non-excretory functions. (Table 1.).

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Table 1. Clinical indicators depending on the stage of CKD

Indicators		CKD stage, n = 120							
		I, n=69 (57,5%)		II, n=21 (17,5%)		III, n=12 (10,0%)		IV, n=18 (15,0%)	
		n	%	n	%	n	%	n	%
gender	male	34	49,3	7	33,3	5	41,7	7	38,9
	female	35	50,7	14	66,7	7	58,3	11	61,1
Age of disease onset									
from 1 to 5 years		17	24,6	5	23,8	2	16,7	3	16,7
from 5 to 10 years		30	43,5	11	52,4	6	50,0	10	55,6
≥10 years		22	31,9	5	23,8	4	33,3	5	27,8
Duration of the disease									
to 1 year		5	7,3	3	14,3	1	8,3	-	-
from 1 to 5 years		21	30,4	1	4,8	4	33,3	3	16,7
from 5 to 10 years		23	33,3	5	23,8	2	16,8	6	33,3
≥10 years		20	29,0	12	57,1	5	41,7	9	50,0
HbA1c ≤7,5%		22	31,9	5	23,8	1	8,3	-	-
HbA1c >7,5%		47	68,1	16	76,2	11	91,7	18	100,0
Age, years		13,2±3,1		14,5±1,6 p_I=0,07		14,2±2,2 p_I =0,28		14,9±1,6 p_I =0,03	
Age of disease onset, years		7,3±3,7		7,1±3,4		7,9±4,0		6,9±2,8	

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		p_I=0,83	p_I=0,61	p_I=0,67
Duration of the disease, years,	6,1±3,9	7,4±3,9 p_I=0,19	6,2±3,9 p_I=0,94	8,1±3,2 p_I =0,05

Note: pI - reliability in relation to the indicator in the CPD group stage I

When analyzing the indicators of the stage of CKD, depending on the age of onset of the disease, there were no significant differences between the groups examined. When analyzing the duration of the disease, it was revealed that as the duration of the disease increases, the cases of progression of CKD stages III and IV increase.

Analysis of the HbA1c level depending on the stage of CKD showed that even children with diabetes in the stage of compensation (HbA1c ≤7.5%) have CKD stages II (23.8%) and III (8.3%).

The use of the new classification K/DOQI (2012) reveals a decrease in kidney function at earlier stages, in 61.9% of children and adolescents with type 1 diabetes at the stage of NAU, stage II CKD was detected, in 16.7% - Stage III CKD. Also, 28.6% and 75.0% of children and adolescents at the MAU stage have CKD II and CKD stage III, respectively (Table 2.).

Table 2. GFR by stage of albuminuria and CKD

Indicators	CKD stage, n = 120							
	I, n=69 (57,5%)		II, n=21 (17,5%)		III, n=12 (10,0%)		IV, n=18 (15,0%)	
	n	%	n	%	n	%	n	%
NAU(A1)	37	53,6	13	61,9	2	16,7		
NAU(A2)	32	46,4	6	28,6	9	75,0	3	16,7
VPU(A3)			2	9,5	1	8,3	15	83,3
GFR (ml/min/1.73m^2)								
Average indicators	168,9±58,4		78,4±8,6		38,2±5,9		22,8±3,8	

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		p_I=0,0001	p_I=0,0001	p_I=0,0001
NAU(A1)	181,6±61,4	80,6±7,5 p_I=0,0001	45,1±9,5 p_I=0,0001	
MAU(A2)	154,1±51,8	76,4±10,6 p_I=0,0001	36,6±4,6 p_I=0,0001	20,3±2,4 p_I=0,0001
VPU(A3)		70,6±5,2	38,2±5,9 p_{II}=0,0001	23,3±3,9 p_{II}=0,0001

Note: pI - reliability in relation to the indicator in the group CPD stage I; pII - reliability in relation to the indicator in the group of CPD stage II. NAU - normoalbuminuria, MAU - microalbuminuria, VPU - severe proteinuria.

Studies have shown that 69 (57.5%) patients with type 1 diabetes have a high and optimal GFR CKD Ist (> 90 ml/min/1.73 m^2). The average GFR was 168.9 ± 58.4 ml/min/1.73 m2 (Me 157.2; IQR 126.2-200.1).

An insignificant decrease in the GFR of CKD IIst (60-89 ml/min/1.73m^2) was detected in 21 (17.5%) patients, the average GFR was 78.4 ± 8.6 ml/min/1.73m2 (Me 78.7 ; IQR 74.3-87.4). Moderate decrease in GFR CKD IIIst. (59-30 ml/min/1.73 m^2) is observed in 12 (10.0%) patients, the average GFR was 38.2 ± 5.9 ml/min/1.73 m^2 (Me 38.3; IQR 33.5 -40.5). Grade IV CKD (15-29 ml/min/1.73 m2) was detected in 18 (15.0%) patients. GFR averaged 22.8 ± 3.8 ml/min/1.73 m^2 (Me 22.6; IQR 19.7-26.8).

In the examined group of patients with type 1 diabetes, CKD Vst. (<15 ml/min/1.73 m^2) was not detected.

Thus, in the majority of the examined children (75.0% OR 9.0; 95% CI 5.02-16.1; p <0.0001) children and adolescents with type 1 diabetes are classified as grades I and II. Chronic kidney disease according to the K/DOQI recommendation (2012).

When analyzing the GFR data depending on the stage of albuminuria and CKD, it was revealed that even at the stage of normoalbuminuria, when there are no clinical signs of the development and progression of diabetic nephropathy, the GFR level can be significantly reduced in relation to the CKD stage I group in 61.9%.

Analysis of the distribution of the ACE gene showed that 49 (40.8%) are carriers of genotype II, I/D genotype occurs in 28 (23.4%) and DD genotype was found in 43 (35.8%) patients with type 1 diabetes (Table 3.).

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Table 3. Clinical indicators depending on I/D polymorphism of the ACE gene

Indicators		Genotype					
		II n=49(40,8%)		ID n=28(23,3%)		DD n=43(35,8%)	
		n	%	n	%	n	%
Gender	Male	25	51,0	12	42,9	16	37,2
	Female	24	49,0	16	57,1	27	62,8
Age of disease onset							
from 1 to 5 years		15	30,6	3	10,7	9	20,9
from 5 to 10 years		20	40,8	13	46,4	24	55,8
≥10 years		14	28,6	12	42,9	10	23,3
Duration of the disease							
to 1 year		4	8,2	3	10,7	2	4,6
from 1 to 5 years		12	24,5	10	35,7	7	16,3
from 5 to 10 years		15	30,6	10	35,7	11	25,6
≥10 years		18	36,7	5	17,9	23	53,5
Age, years		13,3±3,2		13,3±2,6 p_I=1,0		14,6±1,8 p_I=0,02	
Age of disease onset, years		6,9±3,8		8,4±3,7 p_I=0,10		6,9±3,0 p_I=1,0	
Duration of the disease, years		6,7±4,0		4,9±3,7		7,8±3,4	

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			p_I=0,06		p_I=0,16	
NAU(A1)	29	59,2	11	39,3	12	27,9
MAU(A2)	20	40,8	14	50,0	16	37,2
VPU(A3)			3	10,7	15	34,9
Albuminuria, mg/ml						
NAU(A1)	13,2±2,8		14,6±3,5 p_I=0,06		31,7±44,9 p_I=0,005	
MAU(A2)	29,8±15,3		27,9±14,6 p_I=0,60		101,2±50,8 p_I=0,0001	
VPU(A3)	-		83,3±57,7		374,0±189,8 p_I=0,0001	

Note: pI - reliability in relation to the indicator in the group with genotype II; pII - reliability in relation to the indicator in the group with genotype ID; NAU - normoalbuminuria, MAU - microalbuminuria, VPU - severe proteinuria.

Among the examined children and adolescents of the Uzbek population with type 1 diabetes, homozygous carriers of genotypes II (40.8%) and DD (35.8%) of the ACE gene prevail.

Analysis of the distribution of ACE gene genotypes depending on the onset of the disease showed the absence of statistically significant differences between groups with different ages of onset of the disease and the ACE gene polymorphism.

When analyzing the distribution of ACE gene polymorphism on the duration of the disease, it was revealed that the occurrence of ACE gene polymorphic alleles did not significantly differ between groups, i.e. in all groups with different duration of the disease, the occurrence of genotypes is identical.

The majority of 46 (66.7% OR 4.0; 95% CI 1.97-8.12; p = 0.0002) examined with stage I CKD had genotype II. In patients with stage II. CKD in a similar percentage (66.7% OR 4.0; 95% CI

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IMPACT FACTOR
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OCLC - 1121105510

1.11-14.4; p = 0.06) had the DD genotype (Table 4.).

Table 4. The incidence of ACE gene polymorphism and the level of GFR depending on the stage of CKD

Stages of CKD / genotype	I st.,n=69		II st.,n=21		III st,n=12		IV st. ,n=18	
	abc	%	abc	%	abc	%	abc	%
II	46	66,7	3	14,3				
ID	23	33,3	4	19,0	1	8,3		
DD			14	66,7	11	91,7	18	100
GFR (ml/min/1.73m2)								
II	166,9±56,1		77,1±13,5 p_I=0,0001					
ID	172,9±63,8		77,3±9,6 p_I=0,0001		38,2			
DD			79,0±8,0		38,2±6,2 p_{II}=0,0001		22,8±3,8 p_{II}=0,0001	

Note: pI - reliability in relation to the indicator in the group CPD stage I; : pII - reliability in relation to the indicator in the group of CPD stage II.

Among patients with IIIst. Most CKD (91.7%) were carriers of the DD genotype, while in patients with stage IV. No cases of CKD allele I (genotypes ID and DD) were observed and all patients (100%) were carriers of the DD genotype, which once again proves the importance of the role of ACE gene polymorphism in the development and progression of CKD in type 1 diabetes in children and adolescents.

The average GFR in patients with genotype II averaged 161.4 ± 58.6 ml/min/1.73 m^2 (Me 151.0; IQR 124.7-195.4), in carriers of the heterozygous genotype - 154.4 ± 70.7 ml/min/1.73 m^2 (Me 135.0; IQR 110.7-181.7), in

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IMPACT FACTOR
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patients with the DD genotype it was 45.0 ± 25.4 ml/min/1.73 m^2 (Me 33.6; IQR 24.0-74.2).

At the same time, the carriage of the DD genotype correlated with the severity of CKD ($r = 0.66$; $P < 0.05$). Consequently, the presence of the DD genotype predisposes an increased risk of developing and progression of CKD, while genotype II is a predictor of the development and progression of CKD in type 1 diabetes in children and adolescents.

DISCUSSION

We found that as the duration of diabetes increases, the cases of progression of CKD stages III and IV increase, which coincides with the literature data [Semidotskaya Zh.D., 2010]. No dependence of the CKD stage on the age of onset of the disease was found.

A decrease in CKF was observed in almost a third (31.7%) of children and adolescents with a disease duration of up to 5 years. A similar number (31.6%) of children and adolescents with type 1 diabetes showed a decrease in GFR, which corresponds to CKD stages II, III, and IV.

Intensive glycemic control significantly reduces the risk of microvascular disorders in both type 1 and type 2 diabetes, although the optimal HbA1c level required to prevent the progression of CKD in diabetes has not yet been determined. According to Oh S. et al. [2011] HbA1c level <6.50% is associated with a reduced risk of end-stage CKD, which indicates the importance of glycemic control in patients at high risk of nephropathy progression. The DCCT study in patients with type 1 diabetes also confirmed that Hb A1c <7.5% reduces the risk of DN by up to 55%.

Our analysis showed that even children with diabetes in the stage of compensation (HbA1c ≤7.5%) have CKD stages II (28.6%) and III (4.8%). The duration of the disease in children with HbA1c ≤7.5% was 5.53 ± 4.09 years (Me 5.0; IQR 2.0-10.0 years).

The modern classification of CKD (K/DOQI, 2012) contributes to the detection of renal dysfunction in the early stages and allows timely correction of therapy and an improvement in the prognosis of patients.

The results of our study showed that in a significant part of children and adolescents with type 1 diabetes, even at the stage of NAU and MAU, patients with II (61.9% and 28.6%, respectively) and III (16.7% and 75.0 %%) stage of CKD.

Genetic factors, including ethnic or interpopulation differences, play a significant role in the pathogenesis of CKD. In recent years, much attention has been paid to the study of the influence of genetic polymorphisms of the ACE gene on the development of renal complications [Elshamaa M., 2011; McClellan W. 2010; Shanmuganathan R., 2015; Tsai J., 2010].

We found that in children and adolescents of the Uzbek population with type 1 diabetes, homozygous carriers of genotypes II (40.8%) and DD (35.8%) of the ACE gene predominate. For the first time, it was revealed that in children and adolescents with type 1 diabetes in the Uzbek population at stage III CKD, the

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frequency of the DD genotype is 91.7%, and at stage IV CKD, the frequency of the DD genotype is 100%. No cases of stage V CKD were observed among the examined individuals.

A direct correlation was found between the carriage of the DD genotype and the severity of CKD ($r = 0.66$; $P < 0.05$).

Our results are consistent with research data that link the D allele of the ACE gene with the incidence and progression of chronic (glomerular and tubulointerstitial) kidney diseases [Akman B., 2009; Morsy M., 2011].

Thus, the recommendations of K/DOQI (2012), in connection with the ACE gene polymorphism and the calculation of GFR, made it possible to re-evaluate the frequency of renal damage in children and adolescents with type 1 diabetes in the Uzbek population. The study showed that the development and progression of CKD in children and adolescents with type 1 diabetes are associated with I/D polymorphism of the ACE gene, while the DD genotype acts as a marker of CKD progression.

CONCLUSIONS

1. The use of the new classification K/DOQI (2012) reveals a decrease in kidney function at earlier stages, in 61.9% of children and adolescents with type 1 diabetes, even at the NAU stage, a GFR of 80.6 ± 7.5 ml/min/1.73m^2, which corresponds to stage II of CKD and 16.7% have a GFR of 45.1 ± 9.5 ml/min/ 1.73m^2, which corresponds to stage III of CKD. Also, 28.6% of children and adolescents at the MAU stage have CKD II, 75.0% of CKD stage III, respectively.
2. The analysis shows that a decrease in CKF can be observed even with the duration of the disease up to 5 years (38 children and adolescents with type 1 diabetes - 31.7%). Among children and adolescents with type 1 diabetes, 31.6% (12 patients) showed a decrease in GFR, which corresponds to CKD stages II, III, and IV.
3. The frequency distribution of the ACE gene genotypes in children and adolescents with type 1 diabetes was characterized by a significant prevalence of the DD genotype associated with the degree of GFR decline, which confirms the presence of genetic factors in the development of CKD. ACE I/D polymorphism is a molecular genetic marker of susceptibility to the development of CKD type 1 diabetes in children and adolescents.

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