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SIGNIFICANCE OF ALDOSTERONE-SYNTHESIS GENE POLYMORPHISM IN THE DEVELOPMENT OF FIBROSIS PROCESSES IN CARDIORENAL SYNDROME DEVELOPED ON THE BASIS OF CHRONIC HEART FAILURE

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ABSTRACT: In this article, the importance of aldosterone-synthesis gene polymorphism in the development of fibrosis processes in cardiorenal syndrome developed on the basis of chronic heart failure is studied. The obtained results showed that the C344T polymorphism of the CYP11B2 gene in chronic heart failure is consistent with the TT genotype and the occurrence of cardiorenal syndrome as a result of the T allele, and the TT genotype is consistent with the severe course of the disease. Based on different hemodynamic types of CHF, in patients with advanced cardiorenal syndrome, CYP11B2 gene C344T polymorphism carriers of the SS genotype had lower serum aldoterone levels than patients with ST and TT genotypes.

KEYWORDS: chronic heart failure, cardiorenal syndrome, aldosterone, aldosterone synthetase gene, CYP11B2 gene.

INTRODUCTION

Despite the progress made in research on the pathogenesis and progression of chronic heart failure (CHF), as well as the widespread use of effective drugs in practice, it remains one of the current problems of medicine as the most common, progressive and fatal complication [14, 15].

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In recent years, the term cardiorenal syndrome has been used when a patient has simultaneous heart and kidney dysfunction/insufficiency [7]. Cardiorenal syndrome is one of the comorbid conditions aggravating the course of CHF. In this case, the patient may have primary kidney disease leading first to kidney and then heart dysfunction/failure, or heart disease first leading to heart disease and then developing heart and kidney dysfunction/failure as a result [5]. Hemodynamic, neuroendocrine mechanisms [4], renin-angiotensin-aldosterone, sympatho-adrenaline systems [2], oxidative stress, inflammation, apoptosis, anemia [6] and other factors are important in its occurrence and development.

Aldosterone is a mineralocorticoid hormone and is produced mainly in the cortex of the adrenal gland under the influence of angiotensin II. It is also present in the walls of blood vessels, brain, heart, and adipose tissue, and its autocrine and paracrine effects are related to this process. In recent years, there are a number of data confirming that it is synthesized in kidney tissues, including podocytes [3; 10].

In various pathological conditions, aldosterone production is increased as a result of the activation of aldosterone receptors. This causes the body to retain water, increase blood pressure, and increase swelling syndrome. Aldosterone receptors are present not only in the kidney, but also in the myocardium, fibroblasts, and vascular endothelium [11; 13; 16]. Aldosterone increases the synthesis of collagens and causes the proliferation of fibroblasts due to a hypothetical mechanism that is still unknown to these receptors [11; 16]. In experiments conducted on rats, it has been proven that myocardial fibrosis around coronary arteries occurs due to increased production of type I and III collagens by aldosterone and angiotensin II. Aldosterone stimulates collagen synthesis through I-type corticoid receptors in cultured heart fibroblasts [8; 16]. In addition, aldosterone induces inflammatory processes limited to the endothelium of the medium and small vessels of the heart, perivascular areas of the myocardium. It also increases the expression of angiotensin-converting enzyme messenger RNAs in myocardiocytes. In addition to the above, aldosterone increases the effect of the renin-angiotensin system by increasing the number of angiotensin II I-type receptors in the cardiovascular system [9]. In addition, aldosterone has different effects on various organs and systems as follows: it reduces the reabsorption of sodium and water in the renal tubules, activates the sympatho-adrenal system by exerting a neurohumoral effect and reduces the effect of the parasympathetic system; stimulates the action of fibroblasts in the myocardium and enhances collagen synthesis; causes endothelin proliferation and perivascular fibrosis in vessels and weakens baroreflexes.

Aldosterone gene (CYP 11 V2) aldosterone synthase 8q22. mapped on the chromosome. It is located next to the 11b - hydroxylase gene [1]. The aldosterone synthase gene contains 9 exons and spans about 7,000 base pairs of DNA. CYP 11 V2 gene is linked to CYP 11 V1. These two genes show 93% homology to each other and are both encoded on the aforementioned chromosome. Aldosterone synthase belongs to the superfamily of cytochrome R 450 enzymes. Being a monooxygenase protein, it participates in the metabolism of drugs and the synthesis of cholesterol, steroids and other lipids.

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Adrenocorticotropic hormone is believed to be important in the control of aldosterone as it stimulates the synthesis of 11-deoxycorticosterone, which is considered the initial substrate of aldosterone synthase enzymatic action. The region of DNA controlling the CYP 11 V2 gene where the cytosine (C) to thymine (T) 344 position occurs is called the C (-344) T genetic marker. C/C, C/T and T/T genotypes of this gene are distinguished [10, 12].

Therefore, the study of the importance of aldosterone-synthesis gene polymorphism in the development of fibrosis processes in cardiorenal syndrome developed on the basis of CHF is not only scientific, but also of important practical importance.

The aim of the research: to study the importance of polymorphism of the aldosterone-synthesis gene in the development of fibrosis processes in cardiorenal syndrome developed on the basis of chronic heart failure.

Research source and methods. Research source and methods As a research source, a total of 120 patients diagnosed with CHF and who developed cardiorenal syndrome, who were treated in 2020-2022 in the cardiology, cardioreanimation and cardiorehabilitation departments of the former 3rd clinic of the Tashkent Medical Academy, the current multidisciplinary clinic of the Tashkent Medical Academy, were taken. They were divided into 3 groups according to their clinical and hemodynamic status and ExoKG examination results, and the first group consisted of 40 people (average age 58.4 ± 0.8; 13 - CHF II FS, 9 men and 4 women; 27 - CHF III FS, 15 men and 12 women) patients with low left ventricular ejection fraction (LVEF) (< 40%), the second group consisted of 40 people (average age 56.1 ± 0.85; 16 people – CHF II FS, 12 men and 4 women; 24 – CHF III FS, 11 men and 13 women) LVEF partially reduced (41 – 49 %) patients with CHF, the third group consisted of 40 (mean age 55.1± 0.6; 19 – CHF II FS, 13 men and 6 women; 21 patients – CHF III FS, 13 men and 8 women) were patients with CHF with preserved (> 50%) LVEF. 40 practical healthy volunteers were taken as a control group.

We followed the following in the selection of patients with cardiorenal syndrome at CHF in scientific work:

1. One-night albuminuria - proteinuria ≥ 10 mg;
2. Changes in urine sediment - erythrocyturia (hematuria), cylindruria;
3. Tubular dysfunction - glucosuria in the absence of hyperglycemia;

Also, the presence of any of the above-mentioned markers (albuminuria/proteinuria, pathological deposits in urine, morphological changes) confirming kidney damage for three months or more was taken into account when determining SBK.

In our study, we observed patients who fell into C 1, C 2 and C 3a category of SBK. In the three groups observed above based on hemodynamic types, the categories of patients diagnosed with SBK were the same number.

In the patients under observation, laboratory-instrumental and functional tests were performed initially - on 1-3 days of hospitalization, and the next test was performed after 6 months of prospective observation. Initially, all patients' complaints, anamnesis were collected and an objective examination was conducted. Then they were subjected to a general analysis of blood and urine, general clinical, biochemical and blood coagulation system analyses, lipid spectrum, quantitative indicators of aldosterone in the blood serum by immunoenzyme analysis, the number

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of aldosterone synthase gene polymorphisms was determined by polymerase chain reaction (DNA genomes were separated and gene polymorphisms were genotyped).

The results obtained in the study were statistically processed, the mutual harmony and interdependencies and differences between the groups were determined, and summary information and practical recommendations were developed.

MS Excel (2016) package computer program was used for statistical processing of the data obtained in the study. Arithmetic mean and standard deviation (M±m) of indicators presented in all tables were calculated. The reliability of differences between groups was determined using Student's criterion for odd and even differences.

Determination of aldosterone in blood serum. The amount of aldosterone in blood serum was determined by immunoenzymatic analysis using the reagents "DBC Aldosterone ELISA" (Canada).

Determination of aldosterone synthase gene polymorphism 5 ml of venous blood from all patients was taken in a special test tube (anticoagulant liquid was added) and the samples were stored frozen in a refrigerator at -20°C. First, the leukocyte mass was precipitated from the frozen sample using a special method, and then their lysis was performed in TE-buffer using protease and sodium dodecylsulfate. Then, keeping the temperature regime at 42°C, the cell products were thawed in a thermostat for 12 hours. Then the DNA genome was extracted from the cell lysate step by step: in the first step, phenol with hydrochloric acid in a ratio of 1:1, in the second step, in the same ratio of phenol with chloroform, and in the last step, chloroform was added again. The extracted DNA samples were then washed with 96% ice-cold ethanol, dried to ethanol odor, and dissolved in buffer solution for storage in a refrigerator at -20°C.

Aldosterone synthase gene C / C, C /T and T/T genotypes were performed by polymerase chain reaction, and the main products of the reaction were recorded in real time based on the discrimination analysis of alleles in a high-speed amplifier. DNA fragments were visualized by passing ultraviolet light from a special instrument. To assess the quality of the genotyping process, 10% of the samples were retested to ensure 100% accuracy.

Results. In our study, we studied the importance of candidate genes in the development of fibrosis processes in patients with cardiorenal syndrome developed on the basis of different hemodynamic types of CHF. When TT, TC, and CC genotypes of C344T polymorphism of CYP11B2 gene were found in patients with developed cardiorenal syndrome based on CHF, their prevalence was 53.3%, 38.3%, and 8.3%, respectively. In the control group, the genotypes of C344T polymorphism were 10% - TT, 42.5% - CT and 47.5% - CC. In patients with cardiorenal syndrome, the S allele of this gene C344T polymorphism was found in 37.5% of cases, and the T allele in 62.5% of cases, while in the control group, these indicators were found in the opposite proportion, i.e., C allele in 68.7%, T allele in 31.3% of cases (1 - table).

Table 1

Prevalence of alleles and genotypes of CYP11B2 gene C344T polymorphic marker in patients with cardiorenal syndrome and controls

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Alleles and genotypes	The number of occurrences of alleles and genotypes				RR	95% CI	OR	95% CI
	CHF patients		Control group					
	abs.	(%)	abs.	(%)				
C	66	37,5	55	68,7	0,63	0,487; 0,809	0,40	0,241; 0,677
T	110	62,5	25	31,3	2,032	1,463; 2,823	3,790	2,107; 6,815
C/T	46	38,3	17	42,5	0,90	0,589; 1,381	0,84	0,407; 1,740
T/T	64	53,3	4	10,0	5,33	2,074; 13,717	10,2	3,446; 30,700
C/C	10	8,3	19	47,5	0,175	0,089; 0,345	0,1	0,041; 0,246

Note – Abbreviations are for this and subsequent gene tables: RR (English - relative risk) - indicator >When 1, the relative risk means that this group is more likely to develop the disease than the control group; OR (English - odds ratio) - indicator >When 1, the relative chance means that this group is more likely to develop the disease than the control group; CI (English - confidence interval) 95% - confidence is 95%, where both indicators are greater or less than 1, the reliability of indicators is $p<0.05$; $\chi 2$ – xi square is the method chosen to differentiate between the theoretical and practical occurrence of quality marks in groups, the higher its index, the higher the degree of actual occurrence of quality marks.

TT genotype and T allele in patients with cardiorenal syndrome compared to the control group, respectively (10% vs. 53.3%) 5.3 [OR - 10.2; C.I.- 3.446 – 30.700;] and (31.3% vs. 62.5%) 1.9 [OR – 3.790; C.I.- 2,107 – 6,815;] was found twice as often, and it was found that the probability of disease development in their presence is reliably high. CC genotype and C allele in patients with cardiorenal syndrome compared to the control group, respectively (47.5% vs. 8.3%) 5.7 [OR– 0.1; C.I.- 0.041 - 0.246;] and (68.7% vs. 37.5%) 1.8 [OR– 0.4; C.I.- 0.241 - 0.677;] was less frequent and it was found to have a reliable protective effect on the occurrence of the disease. CT genotype is intermediate in the occurrence and progression of the disease, and its reliable association with the risk of developing cardiorenal syndrome has not been determined. 1,1 [OR– 0,84; C.I.- 0,407 – 1,740;].

When studying the prevalence of genotypes and alleles of the CYP11B2 gene C344T polymorphism in different hemodynamic types of the disease in patients with CHF, the following was revealed (Table 2).

Table 2

Alleles and genotypes of CYP11B2 gene C344T polymorphic marker in the low hemodynamic type of LVEF of CHF with cardiorenal syndrome

Alleles and genotypes	The number of occurrences of alleles and genotypes	RR	95% CI	OR	95% CI

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	Group 1 patients		Control group					
	abs.	(%)	abs.	(%)				
C	24	30,0%	55	68,7	0,50	0,345; 0,730	0,29	0,153; 0,544
T	56	70,0%	25	31,3	1,74	1,306; 2,320	3,47	1,839; 6,541
C/T	14	35,0%	17	42,5	0,82	0,473; 1,435	0,73	0,295; 1,797
T/T	21	52,5%	4	10,0	5,25	1,980; 13,923	9,95	2,981; 33,195
C/C	5	12,5%	19	47,5	0,26	0,109; 0,636	0,16	0,051; 0,486

TT genotype [OR – 9.95; C.I. - 2,981 – 33,195;] and T allele [OR - 3.47; C.I.- 1.839 - 6.541);] LVEF low CHF was 5.25 and (70.0% vs. 31.3%) 1.7 times more than the control group values meeting, it became known that the probability of disease development in their presence is reliably high. CC genotype and C allele LVEF in patients with low CHF compared to the indicators of the control group (47.5% vs. 12.5%) 3.8 [OR– 0.16; C.I.- 0.051 - 0.486;] and (68.7% vs. 30.0%) 2.3 [OR– 0.29; C.I.- 0.153 - 0.544;] was less frequent and it was found to have a reliable protective effect on the occurrence of the disease. CT genotype was not reliably associated with this hemodynamic phenotype of the disease 1.2 [OR– 0.73; C.I.- 0.295 – 1.797;].

Table 3

The frequency of occurrence of alleles and genotypes of the C344T polymorphic marker of the CYP11B2 gene in the partially reduced hemodynamic phenotype of LVEF of CHF

Alleles and genotypes	The number of occurrences of alleles and genotypes				RR	95% CI	OR	95% CI
	2nd group of patients		Control group					
	abs.	(%)	abs.	(%)				
C	29	36,3%	55	68,7	0,61	0,434; 0,848	0,38	0,206; 0,709
T	51	63,7%	25	31,3	1,59	1,176; 2,137	2,61	1,410; 4,848
C/T	11	27,5%	17	42,5	0,65	0,348; 1,202	0,51	0,201; 1,308
T/T	20	50,0%	4	10,0	5,0	1,877; 13,322	9,0	2,698; 30,021
C/C	9	22,5%	19	47,5	0,474	0,245; 0,917	0,32	0,122; 0,844

TT genotype of CYP11B2 gene and T allele LVEF in patients with CHF with partially reduced CHF, respectively (10.0% vs. 50.0%) 5.0 [OR – 9.0; C.I. – 2.698 – 30.021;] and (31.3% vs. 63.7%) 2.03 [OR –

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2.61; C.I.- 1,410 – 4,848;] were found twice as often, and it was found that in their presence, the probability of developing this hemodynamic phenotype of the disease is reliably high. In patients with CHF of CC genotype and C allele intermediate phenotype, compared to control group indicators, respectively (47.5% vs. 22.5%) 2.1 [OR– 0.32; C.I.- 0.122 - 0.844;] and (68.7% vs. 36.3%) 1.9 [OR– 0.38; C.I.- 0, 206 - 0,709;] was less frequent and it was found to have a reliable protective effect in the occurrence of the disease. CT genotype was not reliably associated with this hemodynamic phenotype of the disease 1,54 [OR– 0,51; C.I.- 0,201 – 1,308;].

Table 4

The degree of occurrence of alleles and genotypes of the C344T polymorphic marker of the CYP11B2 gene in the preserved hemodynamic phenotype of LVEF of CHF.

Alleles and genotypes	The number of occurrences of alleles and genotypes				RR	95% CI	OR	95% CI
	3rd group of patients		Control group					
	abs.	(%)	abs.	(%)				
C	29	36,3%	55	68,7	0,606	0,434; 0,848	0,38	0,206; 0,709
T	51	63,7%	25	31,3	1,59	1,176; 2,137	2,61	1,410; 4,848
C/T	13	32,5%	17	42,5	0,76	0,431; 1,358	0,65	0,262; 1,621
T/T	19	47,5%	4	10,0	4,75	1,774; 12,721	8,143	2,440; 27,173
C/C	8	20,0%	19	47,5	0,42	0,209; 0,848	0,28	0,102; 0,76

The TT genotype of the CYP11B2 gene and the T allele LVEF in patients with preserved CHF compared to the indicators of the control group, respectively (10.0% vs. 47.5%) 4.75 [OR – 8.143; C.I. – 2,440 – 27,173;] and (31.3% vs. 63.7%) 2.03 [OR – 2.61; C.I. – 1,410 – 4,848;] times more often, it became known that in their presence the probability of developing this hemodynamic phenotype of the disease is reliably high. CC genotype and C allele preserved phenotype in patients with CHF compared to the control group, respectively (47.5% vs. 20.0%) 2.4 [OR– 0.28; C.I.- 0.102 - 0.76;] and (68.7% vs. 36.3%) 1.9 [OR– 0.38; C.I.- 0.206- 0.709;] was less frequent and it was found to have a reliable protective effect on the occurrence of the disease. CT genotype was not reliably associated with this hemodynamic phenotype of the disease 1,3 [OR– 0,65; C.I.- 0,262 – 1,621;].

When comparing the prevalence of CYP11B2 gene C/T polymorphism alleles and genotypes in patients with advanced cardiorenal syndrome based on low, intermediate and preserved hemodynamic types of CHF (Table 5), C allele and CC genotype in group 1 compared to group 2, respectively (by 30% 36.3% against 6.3% (r<0.05) and (12.5% against 22.5%) 10% (r<0.05), compared to group 3 (30% against 36 .3%) occurred reliably less frequently in 6.3% (r<0.01) and 7.5% (r<0.01) (12.5% vs. 20%). T allele and TT genotype were 6.3% (r<0.05) and 2.5% (52.5% versus 50%) in group 1

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than in group 2 (70% vs. 63.7). r<0.05), 13.7% (r<0.01) and (52.5% vs. 47.5%) 5.0% (r <0.01) was significantly more frequent. According to the obtained statistics, the TT genotype and T allele of the C/T polymorphism of the CYP11B2 gene were found to be more common in patients of the 1st group than in the 2nd and 3rd groups of the study. On the contrary, C allele and CC genotype were found in the 3rd group of the study in greater numbers than in the 1st and 2nd groups.

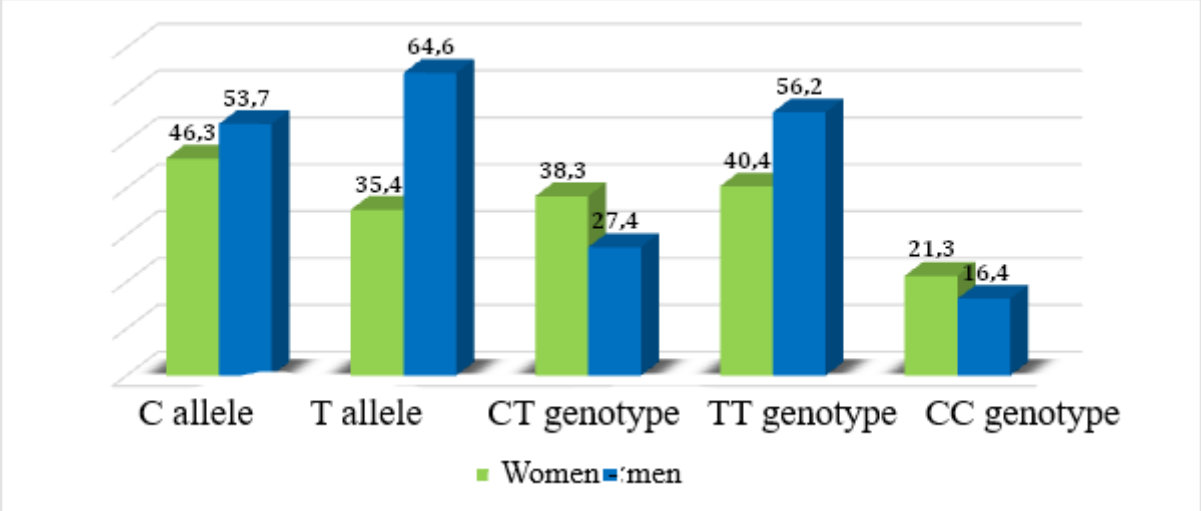
Table 5

The incidence of CYP11B2 gene C/T polymorphism alleles and genotypes in hemodynamic phenotypes of CHF.

Allele and genotype	Meeting of alleles and genotypes, %		P	The meeting of alleles and genotypes,%		P	Meeting of alleles and genotypes, %		P
	1 - group	2 - group		1 - group	3 - group		2 - group	3 - group	
C	30,0%	36,3%	>0,05	30,0%	36,3%	>0,05	36,3%	36,3%	<0,05
T	70,0%	63,7%	<0,05	70,0%	63,7%	<0,01	63,7%	63,7%	<0,05
C/T	35,0%	27,5%	>0,05	35,0%	32,5%	>0,05	27,5%	32,5%	>0,05
T/T	52,5%	50,0%	>0,05	52,5%	47,5%	>0,05	50,0%	47,5%	<0,05
C/C	12,5%	22,5%	<0,05	12,5%	20,0%	<0,01	22,5%	20,0%	<0,05

When studying the alleles and genotypes of the C/T polymorphism of the CYP11B2 gene depending on gender, the following was determined (Fig. 1).

Among the patients with developed cardiorenal syndrome based on CHF involved in the study, T allele of CYP11B2 gene C/T polymorphism and T/T genotype were 29.2% and (56.2%) in men compared to women, respectively (64.6% vs. 35.4%). 40.4%) against 15.8% was found to occur more often. In women, C allele and C/C genotype were 7.4% more frequent than men (46.3% vs. 53.7%) and 14.9% (21.3% vs. 16.4%), respectively.



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1 – fig. Alleles and genotypes of CYP11B2 gene C/T polymorphism in patients with cardiorenal syndrome depending on gender, %

Thus, it was found that the C allele and C/C genotype of CYP11B2 gene C/T polymorphism have a protective effect in both sexes, while the T allele and T/T genotype have a negative effect on the onset and progression of the disease in both men and women.

A comparison of serum aldosterone levels in a section of patients with this genotype was studied (Fig. 2).

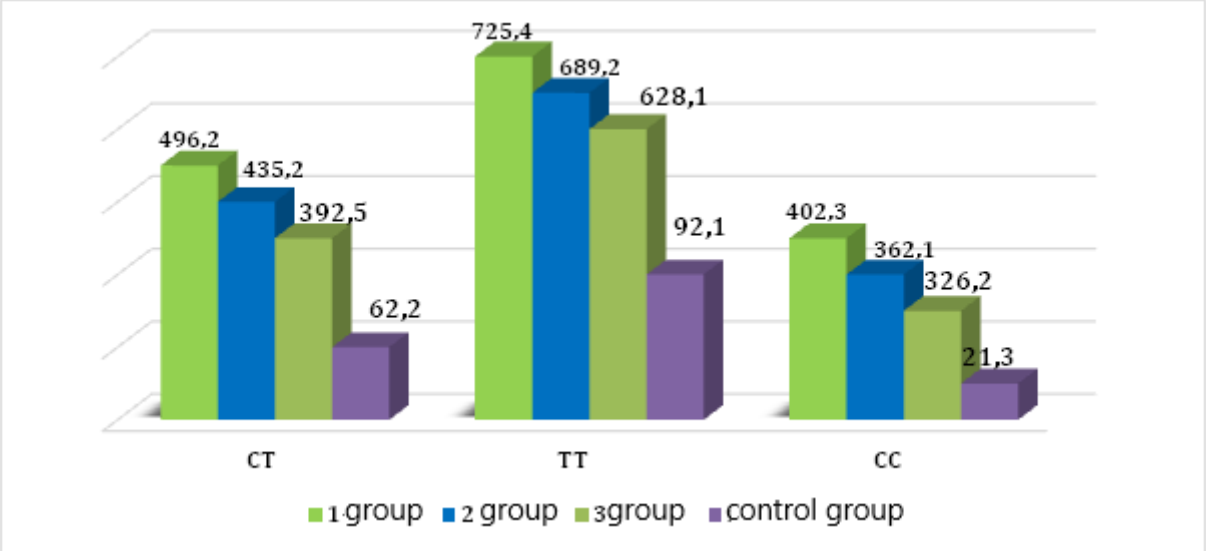

Figure 2. Comparative analysis of serum aldosterone levels in patients with cardiorenal syndrome carrying aldosterone synthase gene C/T polymorphism genotypes and healthy subjects

Comparative analysis of aldosterone levels between groups showed that (Figure 2), CHF with CC genotype of CYP11B2 gene C/T polymorphism has cardiorenal syndrome based on different hemodynamic types, and the control group had lower serum aldosterone levels than patients with CT and TT genotypes. High levels of aldosterone were observed in those with the TT genotype between both groups.

Thus, in the analysis of aldosterone synthase gene polymorphism in the groups, it was found that the probability of developing the disease is reliably high in the presence of the T allele and the TT genotype, and it was found that the quantitative indicator of aldosterone in the blood is reliably high in those with this genotype. It was found that C allele and CC genotype have a protective effect on the development of the disease, and it was noted that the quantitative indicator of aldosterone in the blood serum of the holders of this genotype is reliably lower than the representatives of the other genotypes. The CT genotype occupies an intermediate position in the development of the disease, and its reliable association with the risk of developing cardiorenal syndrome was not determined.

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CONCLUSION

In chronic heart failure, the C344T polymorphism of the CYP11B2 gene, as a result of the TT genotype and the T allele, indicates an unpleasant course of the disease, and the TT genotype (r=0.0023) is in harmony with the severe course of the disease. Based on different hemodynamic types of CHF, in patients with developed cardiorenal syndrome, CYP11B2 gene C344T polymorphism carriers of the SS genotype had lower serum aldoterone levels compared to ST and TT genotype patients (r<0.01).

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