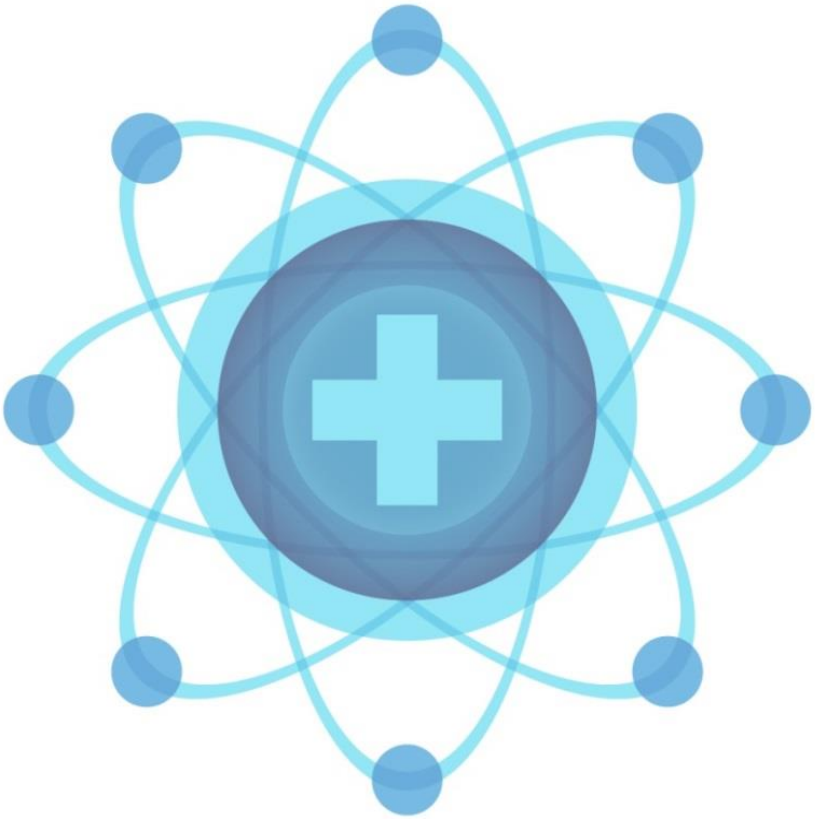

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The role of the renin - angiotensin - aldosterone system in the progression of type 2 diabetes mellitus associated with chronic heart failure.

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Abstract. The purpose of the study is to study the role of a renin-angiotensin-aldosterone system in the progression of type 2 diabetes mellitus (DM2), associated with chronic heart failure (CHF)

Material and research methods. For the period of 2015-2022, 185 patients were determined and selected as an object of study according to the materials of their treatment into Andijan medical and preventive institutions from 30 years and older.
Patients were distributed to 3 groups:
1 group - these are patients with DM 2 +CHF - 65 patients,
Group 2 - these are patients with DM 2without CHF - 60 patients,
Group 3 - these are patients with CHF without DM 2 - 60 patients

Results. To assess the diagnostic significance of this marker, we conducted a correlation analysis of the connection of other indicators affecting the level of aldosterone in blood serum patients with diabetes 2 in combination with heart failure. The correlation analysis conducted by us showed the presence of a direct connection between medium force between the indicators of aldosterone and the age of patients suffering from DM 2 in combination with CHF.

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Thus, in patients with DM 2 with heart failure, an increase in these markers is the most important predictors of an unfavorable forecast for the development of complications up to mortality.

Conclusions. 1. In the study of aldosterone, increased indicators were revealed in all groups, while in patients with heart failure, the indicators are significantly higher than in the group of patients with DM 2In the group of patients with DM2 in combination with CHF, the indicators were the highest, statistically distinguished from indicators of patients with diabetes 2 ($p < 0.001$) and inaccurate in comparison with the CHF group ($P > 0.05$).

2. Renin's levels in groups were significantly higher than the upper limit of the norm lying. At the same time, in the group of DM 2+CHF, the rates of plasma renin statistically reliably exceeded the indicators in the group of patients with isolated diabetes ($p < 0.05$).

3. The results of studies of the interconnection of the plasma level of aldosterone with various clinical characteristics (age, BMI, FV LV, SKF, blood glucose level, HBA1C) of patients with isolated D2 and heart failure are extremely contradictory, and when combined with these pathologies, are practically absent.

Keywords: type 2 diabetes mellitus, chronic heart failure, RAAS

As is known, the main concept for the development of heart failure is excessive activation of the neurohormonal systems, primarily the renin- angiotensin - aldosterone (RAAS) and sympathetic-adrenal systems [1, 2]. According to the authors, RAAS hyperactivation causes the development of atherosclerosis, apoptosis cardiomyocytes , myocardial fibrosis and vascular inflammation [3, 4].

The leading role in the development of myocardial fibrosis and apoptosis is played by angiotensin II (ATII), renin and aldosterone. Thus, ATII, which is formed in the myocardium under the influence of tissue RAAS, increases the permeability of the endothelium of the coronary arteries, improving the delivery of growth factors to their site of action, controls apoptosis processes , increases the synthesis of mitogens

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and growth factors involved in the processes of cardiac remodeling , increases the synthesis of cytokines and other neurohormones (aldosterone, vasopressin, endothelin) [5].

The main role in the regulation of myocardial tissue processes is played by aldosterone (AL), the hyperactivation of which underlies two main pathogenetic patterns. Firstly, this is one of the mechanisms of atherogenesis, namely, due to the development of endothelial dysfunction, a decrease in the bioavailability of nitric oxide, systemic inflammation, and hypercoagulation (stimulation of a plasminogen activator inhibitor) [6]. Secondly, the mechanism of progressive myocardial fibrosis (a decrease in the plasma level of the N-terminal type III collagen peptide, activation of the profibrotic cytokine TGF- beta) and the development of a rigid LV wall are described. This combination of impaired myocardial blood supply and heart fibrosis processes becomes the basis for the development of pathological remodeling of the heart with an outcome in CHF.

Decreased metabolic clearance of aldosteron is an additional important factor in increasing the concentration of aldosteron in the blood of patients with CHF. Aldosterone, in addition to the development of hypokalemia and hypomagnesemia , has other undesirable effects, playing important role in pathophysiology CHF, contributing to increased remodeling of the left ventricle and coronary vessels, endothelial dysfunction, atherosclerosis, and arrhythmic syndrome [Pugliese , 2020]. With a decrease in the concentration of aldosteron fibrinolytic activity is restored , the risk of further thrombosis and the likelihood of developing a second heart attack are reduced. Blockade of receptors for aldosteron accompanied by a decrease in the degree of myocardial fibrosis and the risk of damage vessels, as well as an improvement in endothelial function as a result of an increase in endothelial oxide bioavailability nitrogen [Munzel , 2015].

All of the above motivated the present study.

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The aim of the study is to study the role of the renin- angiotensin - aldosterone system in the progression of type 2 diabetes mellitus associated with chronic heart failure.

Material and research methods. For the period 2020-2022 , we identified and selected 185 patients as an object of study based on the materials of their appeal to medical institutions in Andijan from 30 years of age and older.

The patients were divided into 3 groups:

Group 1 - patients with type 2 diabetes + CHF - 65 patients,

group 2 - patients with type 2 diabetes without CHF - 60 patients,

Group 3 - these are patients with CHF without type 2 diabetes - 60 patients

Inclusion criteria: type 2 diabetes mellitus with CHF, men and women.

Exclusion criteria: pregnant women, children and young people with type 1 diabetes, patients with pathology of the cardiovascular system before the diagnosis of type 2 diabetes, autoimmune thyroiditis (hypothyroidism), stage IV - V chronic kidney disease .

All patients included in the study underwent biochemical studies (ALT, AST, bilirubin, creatinine, glucose, glycated hemoglobin, total cholesterol (CHS), triglycerides (TG), low-density lipoprotein cholesterol (HLDL), high-density lipoprotein cholesterol (HDL-C) on the mindray BA-88A autoanalyzer.

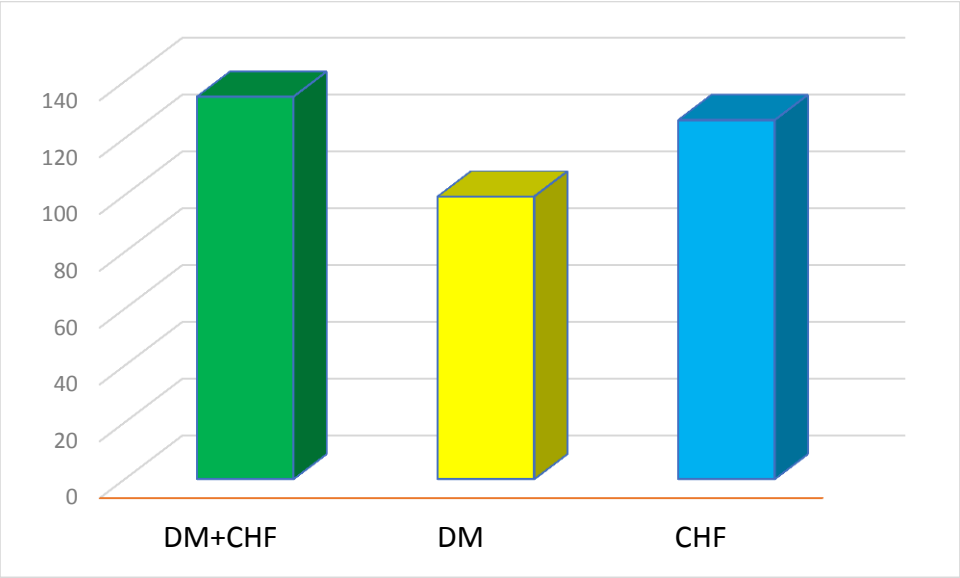
Hormonal studies included the determination of the levels of the N -terminal precursor of natriuretic peptide (NT- proBNP), renin, aldosterone and insulin on the mindray MR - 96A autoanalyzer.

All patients underwent ECG, chest X-ray, Echo-ECG, ultrasound of internal organs.

Statistical calculations were carried out in the Microsoft software environment Windows using Microsoft software packages Excel -2016 and Statistica version 6.0, 2003. The obtained data are reflected in the dissertation as M± m , where M is the mean value of the variation series, m is the standard error of the mean value. The significance of differences between independent samples was determined by the

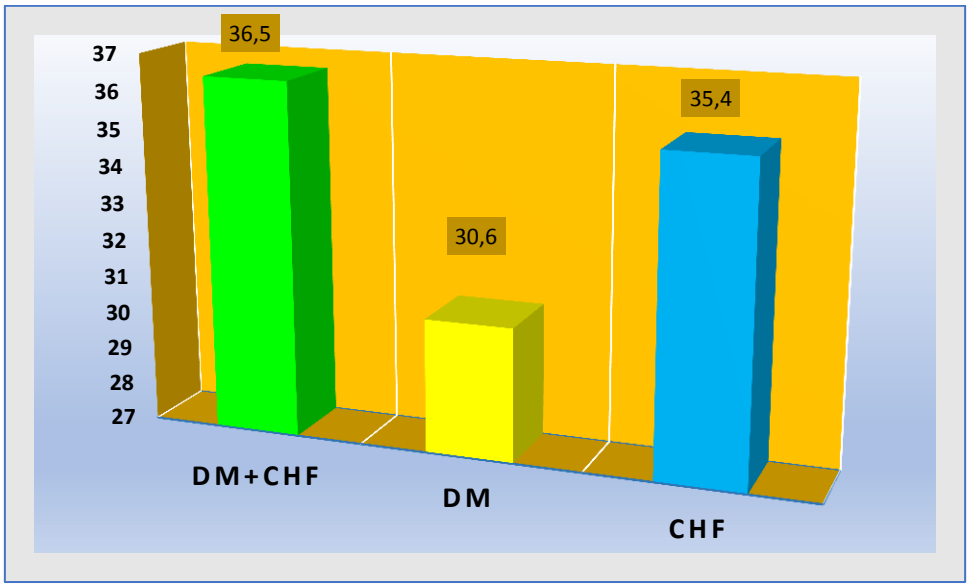
method of Mann-Whitney and Student

Results of the study and their discussion. In the study of aldosterone, elevated levels were revealed in all groups, while in patients with CHF, the indicators were significantly higher (126.4±7.8 pg /ml) than in the group of patients with diabetes (99.5±4.9 pg /ml) (p< 0.01) (Pic. 1).



Rice. 1. The content of aldosterone (pg / ml) in the blood of patients of the studied groups.

In the group of patients with DM in combination with CHF, the indices were the highest (134.6 ± 6.2 pg / ml), statistically significantly different from those of patients with DM (p<0.001) and insignificantly compared with the CHF group (p>0.05) (Pic. 1)



Rice. 2. The content of renin (µIU /ml) in the blood of patients from the studied groups.

The renin levels in the groups were well above the upper limit of normal lying down. However, it should be noted that in the DM+CHF group (36.5±1.9 µIU /ml), plasma renin values were statistically significantly higher than those in the group of patients with isolated DM2 (30.6±1.9 µIU /ml) ($p< 0.05$) , while in the group of patients with CHF, the renin level was also higher (35.4 ± 2.5 µIU/ml) than in the DM 2 group, but lower than in patients with DM2 + CHF, but not statistically significant ($p> 0.05$). (Pic. 2).

The significance of the determination of aldosterone in the diagnosis of CHF in patients with type 2 DM was proved by a comparative analysis conducted in groups of patients with DM2 and DM2 in combination with CHF. The results showed that in the group of patients with type 2 diabetes in combination with CHF in 39 (60.0%) patients, aldosterone levels were higher than normal, while among patients with only type 2 diabetes, there were 11 (18.3%) such patients (Table 1). one). Calculation of the relative chance index (OR) revealed that an increase in the level of aldosterone in the blood increases the risk of developing CHF in patients with type 2 diabetes by 2.25 times ($\chi^2 = 22.6$; $p < 0.001$; OR = 2.25; 95% CI :1.59-3.17).

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A relatively high sensitivity index - 60.0% indicates a corresponding probability of developing CHF in patients with type 2 diabetes with an increase in aldosterone in the blood.

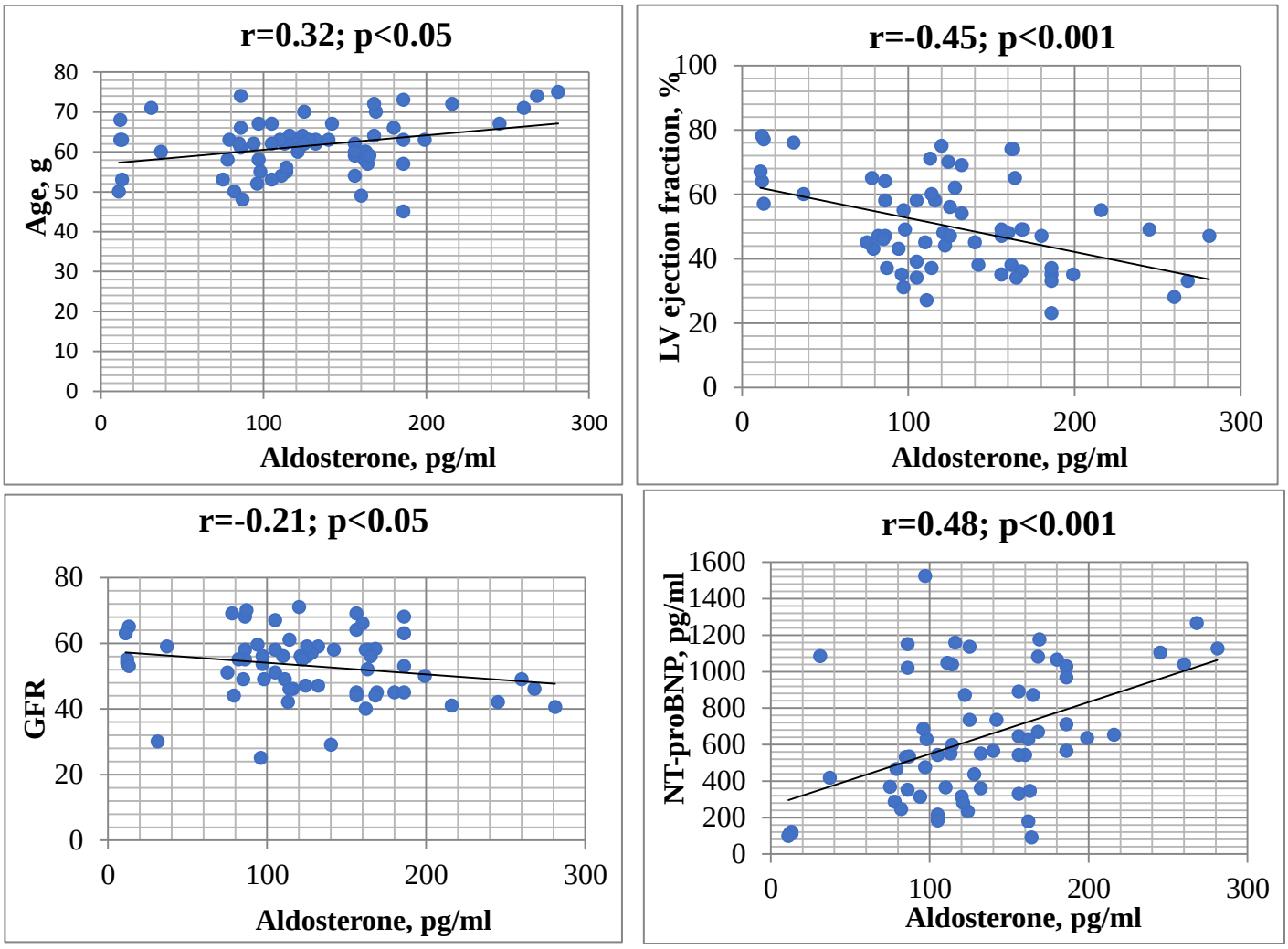
Table 1. Diagnostic value of aldosterone in patients with type 2 diabetes in combination with CHF.

Level aldosterone	**Patients with DM type 2 (*n* = 60)**		**Patients with DM type 2 + CHF (*n* = 65)**		**OR (95% DI)**	**Specificity , _ %**	**Sensorness , %**	χ^2	***p***
	abs	%	abs	%					
Above norms	eleven	18.3	39	60.0	2.25 (1.59-3.17)	82	60	22.6	< 0,001 _ _
Normal	49	81.7	26	40.0					

The results of studies of the relationship between the plasma level of aldosterone and various clinical characteristics (age, BMI, LV EF, GFR, blood glucose level, HbA1c) in patients with isolated type 2 DM and CHF are extremely controversial, and when these pathologies are combined, they are practically absent.

To assess the diagnostic significance of this marker, we conducted a correlation analysis of the relationship of other indicators that affect the level aldosterone in the blood serum of patients with type 2 diabetes in combination with CHF. Nonparametric Spearman 's rank correlation method .

Our correlation analysis showed the presence of a direct relationship of average strength between indicators of aldosterone and age of patients suffering from DM2 in combination with CHF ($r=0.3$, $p < 0.05$) (Pic. 3) .



Pic.3. The relationship of aldosterone with the clinical characteristics of patients with type 2 diabetes and CHF.

In the same group, there was an inverse relationship between aldosterone indices and LV EF (r= - 0.45, p<0.0 0 1). There was a weakly negative correlation between aldosterone and GFR (r = -0.21, p < 0.05). As the level of aldosterone in plasma increases, the concentration of NT proBNP increases. In our study, in patients with type 2 diabetes with CHF, a direct medium-strength correlation between these indicators was revealed.

In patients with type 2 diabetes with CHF, an increase in these markers is the most important predictor of an unfavorable prognosis for the development of complications, up to lethality.

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Significant relationships were found between the level of aldosterone , glycated hemoglobin and blood glucose.

There are a number of neuroendocrine systems that are activated, both in isolated cardiac pathology and in combination with other diseases, in particular type 2 diabetes. One of these systems is the RAAS, the final activation component of which is aldosterone. Conducted by various scientists, clinical studies have shown a multidirectional relationship between the levels of aldosterone and renin in blood plasma.

In our study, it was also important to identify the nature of the dependences of aldosterone and renin parameters in patients with type 2 diabetes in combination with CHF.

Correlation analysis made it possible to establish the presence of a significant weak relationship between renin and the age of patients, rectilinear ($r = 0.25$; $p < 0.05$) and inverse between renin and GFR ($r = -0.28$; $p < 0.05$) (Pic.5.2). Between the level of renin and LV EF, an inverse relationship of medium strength was revealed ($r = -0.36$; $p < 0.05$), while with NT - proBNP and aldosterone there was a direct relationship of moderate strength ($r = 0.55$; and $r = 0.60$, $p < 0.001$, respectively).

In order to study in detail the role of RAAS in patients with type 2 diabetes in combination with CHF, aldosterone and renin parameters were studied depending on the left ventricular ejection fraction (Table 2).

The data presented in Table 2 indicate that the levels of aldosterone and renin increased as the LV ejection fraction decreased.

Table 2.

Levels of aldosterone and renin in patients with DM+CHF depending on the value of the ejection fraction.

indicator	**Patients Subgroups**			**p**
	save PV	PV interval	low EF	
Aldosterone, pg /ml	119.7±8.5	136.6±12.6	151.4±12.3	1-3 < 0.05

Renin, pg /ml	32.4±2.9	43.0±3.4	45.4±3.9	1-2 <0 , 0 5 1-3 <0 , 0 1

Differences in aldosterone levels were statistically significant only between preserved and low LV ejection fractions ($p_{1-3} < 0.05$) . Differences in renin levels were statistically significant between the preserved fraction and the intermediate, as well as low (p_{1-2} <0 , 05 and p_{1-3} <0 , 0 1). Which indicates an unfavorable prognosis for CHF in patients with type 2 diabetes.

Correlation analysis reveals the significance of a particular factor to a greater extent. We have analyzed the relationship between aldosterone and renin with a number of clinical characteristics depending on the LV EF.

Analysis of aldosterone parameters in the subgroup of patients with preserved LV EF showed that the relationship was significant only with BMI, LV EF, GFR and NT- proBNP (r= 0.41 ; r = -0.25 ; r = -0.23 ; r=0.28 , respectively ; p<0.01).

Similar calculations were carried out with renin indices. It was found that there was a direct correlation of medium strength between renin and BMI (r= 0.43, p < 0.05). From the LV EF and GFR in renin, an inverse significant and moderate correlation was revealed (r= - 0.31 and r = - 0.46, p < 0.05, respectively). The most significant statistically significant relationship was found with NT - proBNP and aldosterone (r= 0.52 and r= 0.56, p < 0.001, respectively).

A comparative analysis of aldosterone levels in a subgroup of patients with intermediate LV EF with a number of clinical characteristics was performed. It was found that with a decrease in LV EF, the strength of aldosterone association with age increases (r= 0.62, p < 0.001). The ratios of aldosterone parameters with LV EF and GFR had a negative medium strength relationship (r= - 0.53, p < 0.001 and r= -0.35, p < 0.05, respectively).

was a pronounced direct relationship between the indices of aldosterone and NT - proBNP (r= 0.75, p < 0.001).

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The nature of the relationship between renin parameters and the analyzed characteristics was similar to the correlation of aldosterone with them. Thus, an inverse medium-strength relationship was revealed between renin and LV EF (r = -0.59, p < 0.001). There was a modest direct relationship with age, NT - proBNP and aldosterone (r= 0.44, p < 0.05, r= 0.53 and r= 0.61, p < 0.001, respectively)

In patients with type 2 diabetes in combination with CHF with low LV ejection fraction, aldosterone levels had a significant direct relationship with age and NT-proBNP (r= 0.62 and r= 0.64, p < 0.001, respectively). Aldosterone had a weak inverse relationship with LV ejection fraction (r = -0.28 , p < 0.05). With other clinical signs, the relationship was insignificant or absent.

Analyzing renin parameters in patients with type 2 diabetes with CHF with low LV ejection fraction, similar trends were established that were identified in the analysis of aldosterone parameters in the same subgroup. Thus, the ratio of renin with age, NT - proBNP and aldosterone had a direct significant relationship (r= 0.42, r= 0.68 and r= 0.38 p < 0.001, respectively). Correlation with LV EF and GFR had an inverse weak and moderate relationship (r= -0.27 and r = -0.35 , p < 0.05 , respectively)

Conclusions. 1. In the study of aldosterone, elevated indicators were found in all groups, while in patients with CHF, the indicators were significantly higher than in the group of patients with DM 2. In the group of patients with DM2 in combination with CHF, the indicators were the highest, statistically significantly different from those in patients with DM 2 (p< 0.001) and insignificant in comparison with the CHF group (p> 0.05).

2. Renin levels in the groups were significantly above the upper limit of normal lying. At the same time, in the DM2+CHF group, plasma renin values were statistically significantly higher than in the group of patients with isolated DM2. (< 0,05) .

3. The results of studies of the relationship between the plasma level of aldosterone and various clinical characteristics (age, BMI, LV EF, GFR, blood glucose level, HbA1c) in patients with type 2 diabetes with CHF showed that when

these pathologies are combined with EF and GFR, there is negative feedback, and between the level of CHF biomarker NT- proBNP aldosterone revealed a positive significant correlation.

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