DATA FUSION INTERDISCIPLINARY INSIGHTS INTO BIG DATA, ANALYTICS, AND DECISION-MAKING

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THE ROLE OF TNF-α AND COLLAGEN IV IN THE PROGRESSION OF RENAL DYSFUNCTION AND FIBROUS FORMATION IN PATIENTS WITH CHRONIC HEART FAILURE

N.V.Pirmatova

Tashkent Medical Academy, Uzbekistan

Y.B Bakhronova

Tashkent Medical Academy, Uzbekistan

ABSTRACT: One of the mechanisms for the development of fibrosis in the kidneys and glomerulosclerosis in patients with chronic heart failure (CHF) is the activation of pro-inflammatory cytokines, which lead to the synthesis of profibrotic markers and the progression of fibrosis and sclerosis. It has been established that TNF-α is capable of stimulating left ventricular hypertrophy, increasing the content of CRP, stimulating coagulation, worsening the lipid spectrum of the blood, and most importantly, activating fibroblasts and triggering collagen synthesis, which leads to fibrosis both in cardiomyocytes and glomerulosclerosis in the kidneys[1].

Type IV collagen constitutes the main structure of the basement membrane and mesangial matrix of the glomerular kidney, is a high molecular weight fibrillar protein with a molecular weight of approximately 540 kDa, consists of α3, α4 and α5 chains and, as a rule, is not filtered through the glomerular basement membrane. The determination of collagen IV in urine sediment is of great scientific and practical importance for the purpose of early detection of sclerotic processes in the glomerular membrane of the kidneys in patients with CHF[2,4]. In order to examine what the state of the cytokine-inflammatory state and the structure of basement membrane are in patients with FC II-III CHF, the content of the pro-inflammatory cytokine TNF-α and type IV collagen of the studied patients was examined.

Aim. Evaluation of TNF-α and collagen IV in the progression of renal dysfunction and fibrous formation in patients with chronic heart failure.

Materials and methods The study included 67 patients with functional classes (FC) II-III of CHF of ischemic origin with reduced and mid-range ejection fraction (EF) according to the New York Heart Association (NYHA) classification. The average age was 64.3+ 0.62, 40 (60%) patients were men, 27 (40%) women. Patients were divided into 3 groups according to their treatment tactics. Group I - 22 patients in complex treatment received additional sacubitril + valsartan 50 mg / day, group II - 22 patients in complex treatment with empagliflozin 10 mg / day, group III - 23 patients - a combination of sacubitril + valsartan and empagliflozin.

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Results As can be seen from the data of our study, TNF-α indicators were significantly reduced with a greater effect in the third subgroup of patients with CHF, where a combination of sacubitril/valsartan and empagliflozin was used. In this connection, we can assume that empagliflazin also has an anti-inflammatory effect and, in combination with sacubitril/valsartan, has a pronounced anti-inflammatory, and subsequently anti-fibrotic effect. In the group of patients who received sacubitril-valsartan in combination, TNF-α levels decreased significantly from 13.2 to 8.4 pg/ml ($p<0.05$), in the group of patients who received empagliflozin in combination, the TNF-α level decreased from 12.6 to 8.2 pg/ml ($p<0.05$), in the group where the combination of sacubitril-valsartan and empagliflozin was used, the TNF-α indicator significantly decreased from 12.8 to 5.5 pg/ml ($p<0. 01$). The level of collagen IV in urine is highly negatively correlated with GFR ($r=-0.742$; $p<0.001$).

Conclusion The use of a combination of empagliflozin and sakabutril/valsartan in complex treatment has a beneficial effect on renal filtration, and it can be assumed that the drugs, by stabilizing pathological processes, can slow down the processes of fibrosis formation and glomerulosclerosis in the basement membrane and renal tubules.

KEYWORDS: Chronic heart failure, collagen IV, TNF-α, glomerulosclerosis, renal fibrosis, chronic kidney disease.

INTRODUCTION

One of the mechanisms for the development of fibrosis in the kidneys and glomerulosclerosis in patients with chronic heart failure (CHF) is the activation of pro-inflammatory cytokines, which lead to the synthesis of profibrotic markers and the progression of fibrosis and sclerosis. It has been established that TNF-α is capable of stimulating left ventricular hypertrophy, increasing the content of CRP, stimulating coagulation, worsening the lipid spectrum of the blood, and most importantly, activating fibroblasts and triggering collagen synthesis, which leads to fibrosis both in cardiomyocytes and glomerulosclerosis in the kidneys. Simultaneously with the pro-inflammatory effects, TNF-α has a pronounced pro-atherosclerotic and prothrombogenic effect due to stimulation of fibroblast proliferation, production of metalloproteinases, and accumulation of the main components of the extracellular matrix. In order to examine what the state of the cytokine-inflammatory state is in patients with FC II-III CHF, the content of the pro-inflammatory cytokine TNF-α in the blood of the studied patients was examined.

Figure 1. The level of TFN-α in patients with chronic heart failure in the dynamics of therapy.

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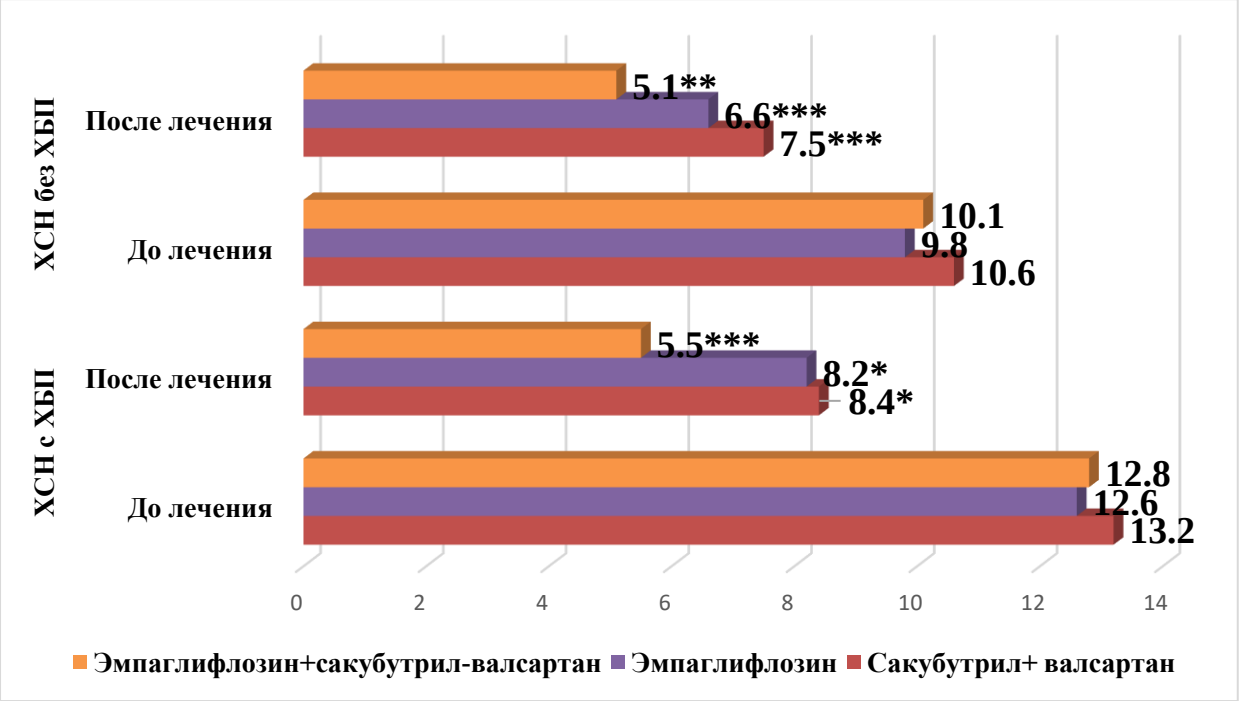

Notes: reliability indicators before and after treatment *-p<0.05; ** p<0.01; *-p<0.001**

The level of TNF-α in the first group of patients with kidney damage was 12.8±1.5 pg/ml. This is almost 2 times higher than normal, which confirms the immunoinflammatory concept of the pathogenesis of CHF. In addition, it can be assumed that the increase in this indicator was also facilitated by the recent systemic Covid-19, which also contributed to the inflammation process. In the second group - the control group, patients with CHF without signs of chronic renal failure, the level of TNF-α was 10.2±0.7 pg/ml. (Fig.2.).

Figure 2. Dynamics of TFN-α in patients with chronic heart failure with chronic kidney disease

Indicators, TNF-α, pg/ml	Sacubitril-valsartan, n= 52	Empagliflozin, n= 53	Empagliflozin + Sacubitril-valsartan, n= 53
Before treatment	13,2±1,3	12,6±1,5	12,8±1,6
After treatment	8,4±1,4*	8,2±1,3*	5,5±1,4**

Notes: reliability indicators before and after treatment *-p<0.05; ** p<0.01; *-p<0.001**

As follows from figure 2, significant positive changes are noted in the dynamics of therapy in the first group of patients with CKD. As mentioned above, the study patients received standard complex therapy, consisting of ACE inhibitors or ARB II, beta blockers, mineralocorticoid receptor antagonists, and loop diuretics as needed. In the group of patients who received sacubitril-valsartan in combination, TNF-α levels significantly decreased from 13.2 to 8.4 pg/ml (p<0.05), in the group of patients who received empagliflozin in combination, the TNF-α level significantly decreased from 12.6 to 8.2 pg/ml (p<0.05), in the group where the combination of sacubitril-

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valsartan and empagliflozin was used, the TNF-α indicator significantly decreased from 12.8 to 5.5 pg/ml (p<0. 01).

TNF-α indicators in the second group of patients who do not have signs of CKD, elevated levels of this marker are also recorded (Figure 3).

Figure 3. Dynamics of TNF-α in patients with chronic heart failure without signs of chronic kidney disease.

Indicators, TNF-α, pg/ml	Sacubitril-valsartan, n= 22	Empagliflozin, n= 22	Empagliflozin + Sacubitril-valsartan, n= 23
Before treatment	10,6±0,8	9,8±0,6	10,1±0,9
After treatment	7,5±0,4**	6,6±0,5***	5,1±0,4***

Notes: reliability indicators before and after treatment *-p<0.05; ** p<0.01; *-p<0.001.**

The average TNF-α level in the second group of patients without renal damage was 10.2±0.7 pg/ml. There is an improvement in the dynamics of the treatment, i.e. decrease in TNF-α levels, in the first subgroup the indicator decreased to 7.5±0.4 pg/ml (p<0.01), in the second subgroup, where patients received empagliflozin from 9.8±0.6 pg/ml significantly decreased to 6.6±0.5 pg/ml (p<0.001), and in the third subgroup from 10.1±0.9 it decreased to 5.1±0.4 pg/ml (p<0.001).

As mentioned above, it has been proven that podocytes are not capable of proliferation and replacement, therefore the progressive loss of these cells in the glomerulus of the kidney entails exposure of the glomerulobasilar membrane and triggers the processes of glomerulosclerosis. As a result of detachment of podocytes from the glomerulo-basilar membrane, they are excreted into the urinary space, where their fragments, nephrin protein and collagen IV are detected as markers of apoptosis and glomerulosclerosis. Type IV collagen constitutes the main structure of the basement membrane and mesangial matrix of the glomerular kidney, is a high molecular weight fibrillar protein with a molecular weight of approximately 540 kDa, consists of α3, α4 and α5 chains and, as a rule, is not filtered through the glomerular basement membrane. In this regard, the determination of collagen IV in urine sediment is of great scientific and practical importance for the purpose of early detection of sclerotic processes in the glomerular membrane of the kidneys in patients with CHF.

As is known, one of the first signs of damage to the glomerular membrane of the glomeruli is albuminuria. In this regard, we determined albuminuria in parallel with collagen IV in the examined patients and the following changes were identified (Fig.4).

Figure 4. Albuminuria in patients with CHF with reduced and moderately reduced ejection fraction (%).

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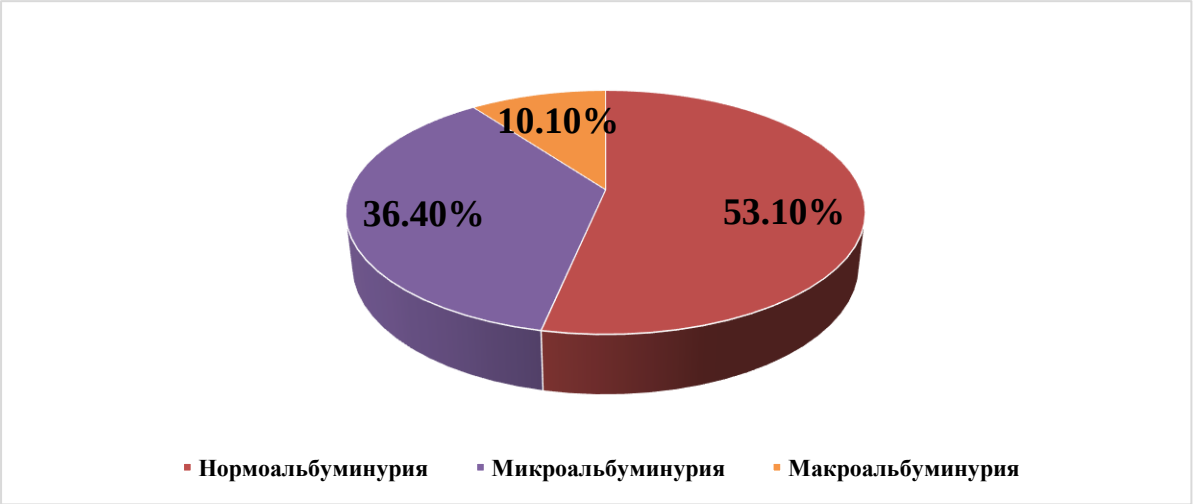

Microalbuminuria was detected in 36.4% of the patients we examined, normoalbuminuria in 53.1%, and macroalbuminuria in 10.1% of patients. As follows from the figure, it was found that almost 2/3 of the patients had albuminuria. That is, it can be assumed that in almost all patients with FC II and III CHF, there is a violation of the permeability of the glomerular basement membrane.

It was found that in those patients who had normoalbuminuria, collagen IV was also detected in the urine, which suggests the important role of the basic excretion of type IV collagen in the urine as an independent predictive factor for the development of glomerulosclerosis with subsequent renal failure. Its presence in the urine of patients with CHF, even with normoalbuminuria, allows it to be considered an early non-invasive marker for diagnosing fibrosis processes in the kidneys.

The differences in the diagnostic value of urinary excretion of collagen and albumin are due to the fact that collagenuria is more associated with the development of renal fibrosis, while albuminuria reflects the permeability of the renal filter. According to our data, collagen excretion is observed in all patients with FC II and III CHF with reduced and moderately reduced EF. These patients are likely to be at risk for further development of renal failure.

Fibrosis of the glomeruli and interstitium of the kidney is characterized by pathological accumulation of collagen IV in these structures; therefore, indicators of collagen turnover, which is an important structural unit of the glomerular membrane matrix, are considered potential diagnostic markers of renal fibrosis.

In the main group of patients with signs of CKD, the content of collagen - Ⅳ was 91.8 ± 2.9 µg/mmol. In the first subgroup of patients who received sacubitril-valsartan as part of complex treatment, the level of collagen-Ⅳ significantly decreased from 91.5±2.6 to 78.6±3.1 µg/mmol ($p<0.01$).

Figure 5. Indicators of collagen-Ⅳ in the dynamics of treatment in patients with chronic heart failure with chronic renal failure.

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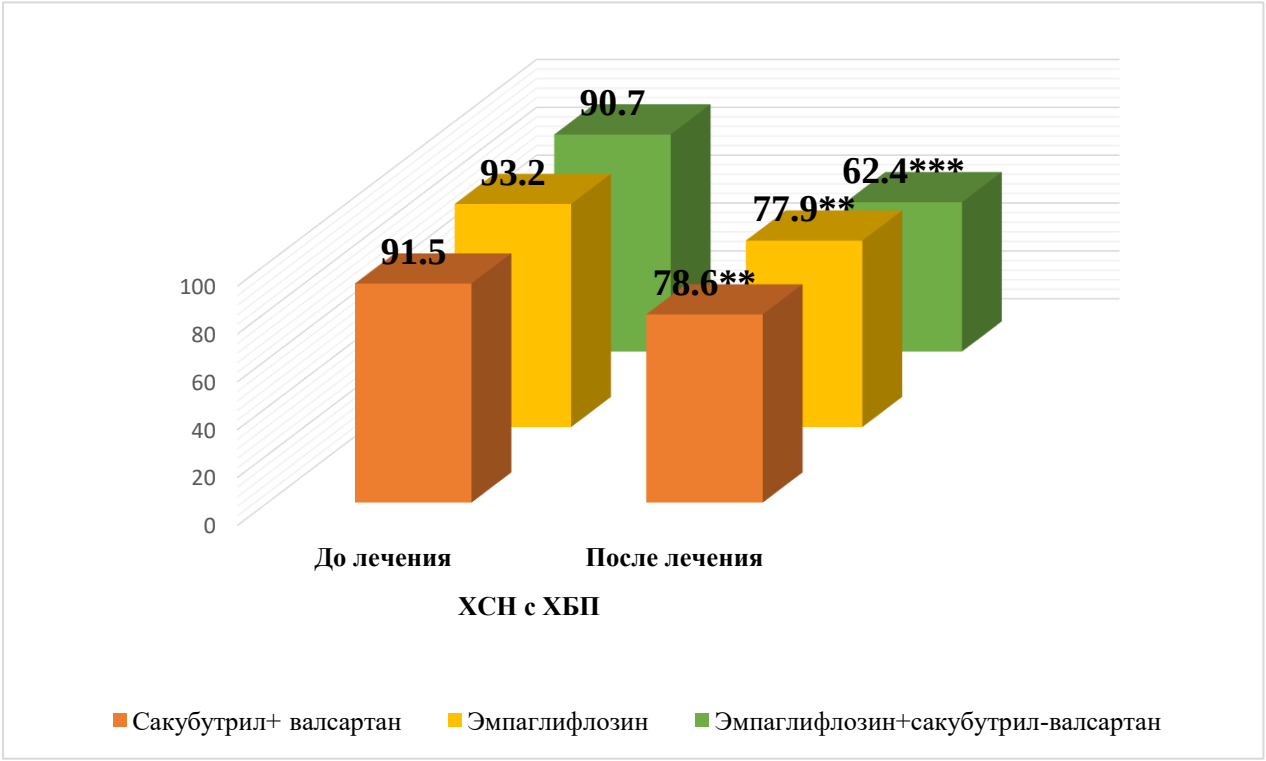
Indicators, collagen Ⅳ, mcg/mmol	Sacubitril-valsartan, n= 52	Empagliflozin, n= 53	Empagliflozin + sacubitril valsartan, n= 53
Before treatment	91,5±2,6	93,2±3,2	90,7±2,8
After treatment	78,6±3,1**	77,9±3,4**	62,4±2,6***

Notes: reliability indicators before and after treatment *-p<0.05; ** p<0.01; *-p<0.001.**

In the second subgroup, those receiving empagliflozin, the collagen-Ⅳ index decreased from 93.2±3.2 to 77.9±3.4 μg/mmol (p<0.01). In the third subgroup of patients receiving a combination of sacubitril-valsartan and empagliflazine, collagen levels decreased from 90.7±2.8 to 62.4±2.6 μg/mmol (p<0.001) (Fig.6).

Figure 6. Collagen level - Ⅳ in urine in patients with chronic heart failure in the dynamics of therapy.



Notes: reliability indicators before and after treatment *-p<0.05; ** p<0.01; *-p<0.001**

As can be seen from the graph (Fig.6) in the main group of patients, there was a more significant improvement in the content of collagen Ⅳ in the urine, that is, the combination of these drugs has a beneficial effect on renal filtration. It can be assumed that the drugs empagliflozin and sakabutril-valsartan, by stabilizing the basal glomerular membrane, can slow down the processes of fibrosis formation in it.

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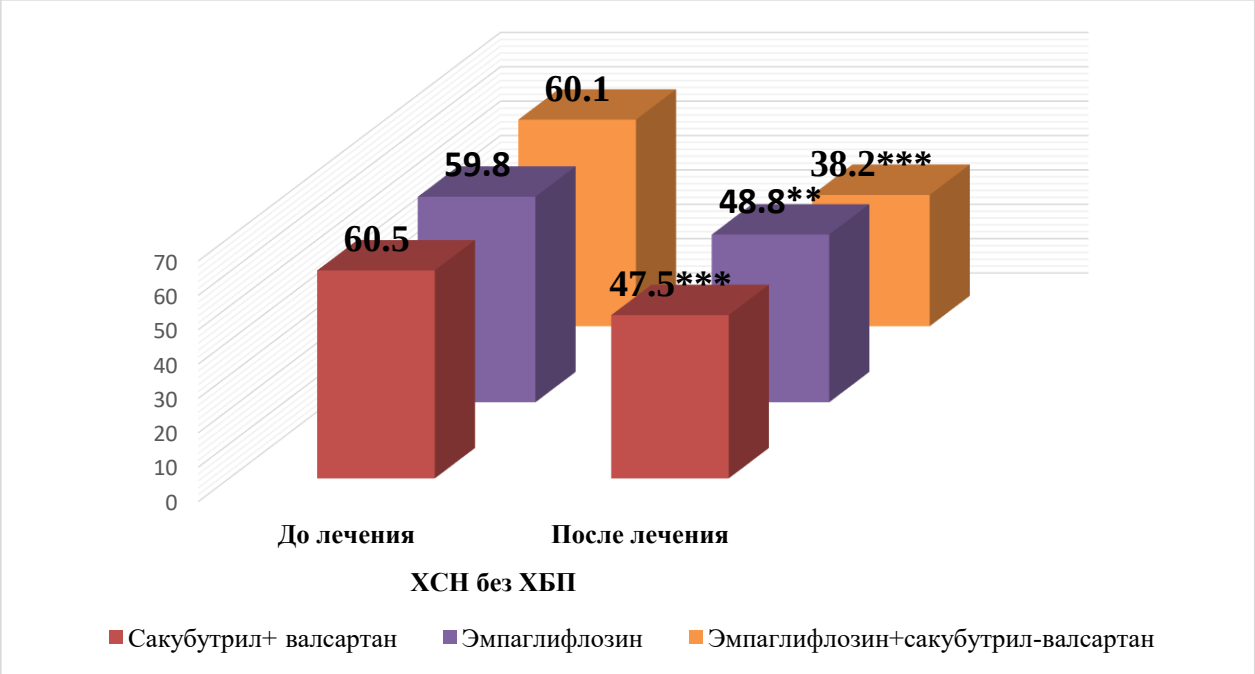
During the experiment the indicators of collagen-Ⅳ in the urine of patients in the second group - the control group, without signs of CKD, its average content was 60.1 ± 2.8 µg/mmol. Of course, this indicator is several times lower than in the group with signs of renal dysfunction, but even though patients in this group have no signs of renal dysfunction, an increase in collagen levels is detected - Ⅳ above normal, that is, the processes of glomerulosclerosis have already begun, although conventional laboratory diagnostic methods did not show changes.

Against the background of the therapy in the first subgroup, the content of collagen-Ⅳ is stabilizing from 60.5±2.8 to 47.5±2.4 µg/mmol ($p<0.001$), in the second subgroup it decreased from 59.8±2.6 to 48.8±2.5 mcg/mmol ($p<0.01$), in the third subgroup, which received a combination of sacubitril-valsartan and empagliflazin, collagen indicators - Ⅳ significantly decreased from 60.1±2.9 to 38.2± 2.4 µg/mmol ($p<0.001$).

Figure 7. Level of collagen-Ⅳ in urine in patients with chronic heart failure in the dynamics of therapy.



Notes: reliability indicators before and after treatment *-$p<0.05$; ** $p<0.01$; *-$p<0.001$.**

Figure 7 shows that the empagliflozin stabilize collagenuria quite effectively. According to Panchapakesan U, Pegg K, it was shown that empagliflozin inhibits the synthesis of profibrogenic and inflammatory factors that are important in the pathogenesis of renal dysfunction. When exposed to empagliflozin on immortalized human kidney cells HK-2, incubated under special conditions, a decrease in the expression of type IV collagen, which affects the synthesis of a number of pro-inflammatory and profibrotic factors, was observed [3].

When determining the urinary excretion of type IV collagen, as well as TNF-α in plasma, some correlations were identified. A significant positive "noticeable" relationship was established with

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nephrinuria (r=0.602; p<0.001), moderately positive with cystatin C (r=0.424; p<0.05) and blood creatinine (r=0.562; p<0.01), and there is also a weak negative relationship with the left ventricular ejection fraction (r = -0.229; p = 0.05) (Fig.8).

Figure 8. Correlation of collagen-IV and TFN-α with some parameters in patients with chronic heart failure of functional classes II-III with reduced ejection fraction.

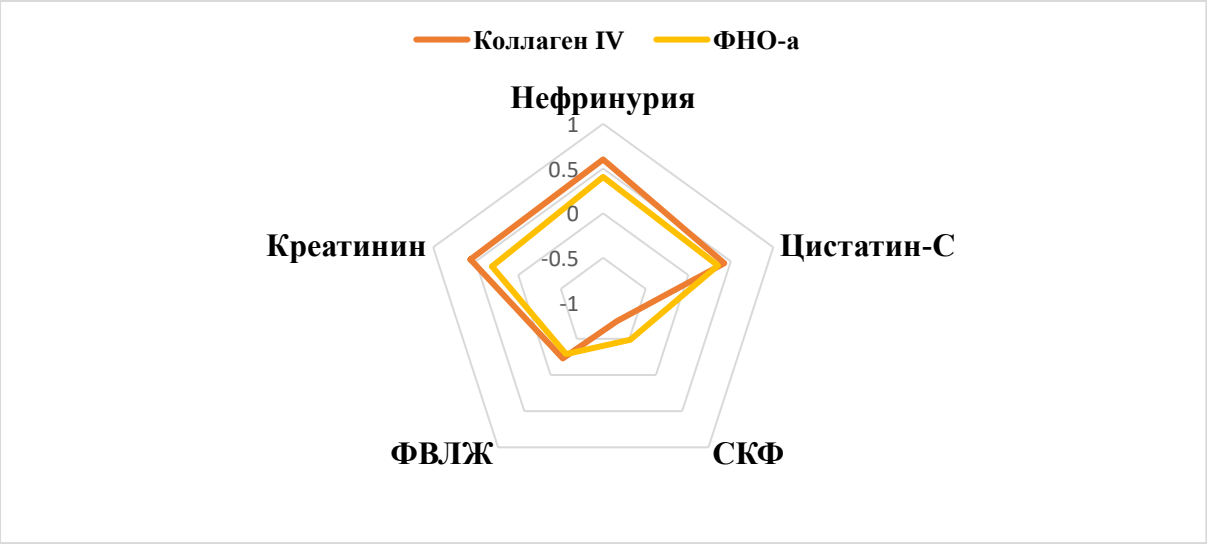
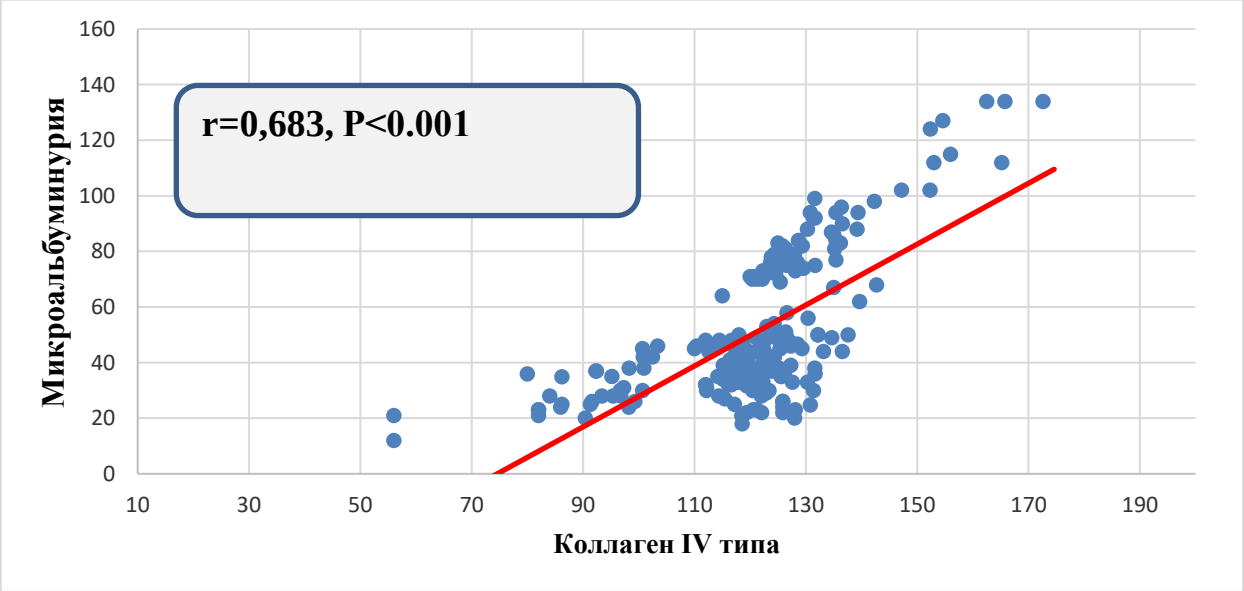


Figure 9. Correlation between collagen-IV and microalbuminuria in patients with chronic heart failure of functional classes II-III with reduced ejection fraction.



A significantly positive association with albuminuria was found (r=0.683; P<0.001) (Fig.9).

Figure 10. Correlation between collagen-IV and glomerular filtration rate in patients with chronic heart failure of functional classes II-III with reduced ejection fraction.

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CONCLUSION

As can be seen from the data of our study, TNF-α indicators were significantly reduced with a greater effect in the third subgroup of patients with CHF, where a combination of sacubitril/valsartan and empagliflozin was used. In this connection, we can assume that empagliflazin also has an anti-inflammatory effect and, in combination with sacubitril/valsartan, has a pronounced anti-inflammatory, and subsequently anti-fibrotic effect. Thus, in the overwhelming number of patients with CHF II and III FC with reduced and moderately reduced EF, collagenuria is detected, which indicates that renal dysfunction and glomerulosclerosis processes have already begun, which begin long before the appearance of albuminuria in the examined patients. The detection of collagen IV in patients whose urine had normoalbuminuria suggests an important role for the basal excretion of this marker as an independent predictive factor for the development of glomerulosclerosis with subsequent renal failure.

The role of collagen IV in patients with FC II and III CHF with reduced and moderately reduced EF, as an early marker of kidney fibrosis, is confirmed by a highly negative correlation with GFR ($r=-0.742$; $p<0.001$), noticeably positive with albuminuria ($r=0.683$; $P< 0.001$) and nephrinuria ($r=0.602$; $p<0.001$). The use of a combination of drugs empagliflozin and sakabutril/valsartan in complex treatment has a beneficial effect on renal filtration, and it can be assumed that the drugs, by stabilizing pathological processes, can slow down the processes of fibrosis formation and glomerulosclerosis in the basement membrane and renal tubules.

REFERENCES

1. Мацкевич С.А, К.С. Атрошенко, М.И. Бельская Дисфункция почек при хронической сердечной недостаточности,Авторы:., ,23.01.2018Муркамилов И.Т., Сабиров И.С., Фомин В.В., Муркамилова Ж.А., Сабирова А.И., Цой Л.Г., Айтбаев К.А., Реджапова Н.А., Юсупов Ф.А. Взаимосвязь параметров центральной гемодинамики и цитокинового профиля при хронической болезни почек в сочетании с цереброваскулярными заболеваниями. Журнал неврологии и психиатрии им. С.С. Корсакова. 2019;119(6):65-71.

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2. Ix JH, Shlipak GM, Chertow GM et al. Association of cystatin C with mortality, cardiovascular events, and incident heart failure among persons with coronary heart disease: data from the heart and soul study. Circulation
3. Okonogi H, Nishimura M, Utsunomiya Y, et al. Urinary type IV collagen excretion reflects renal morphological alterations and type IV collagen expression in patients with type 2 diabetes mellitus. Clin Nephrol 2001;55(5):357-364. PubMed PMID: 1 1393380.
4. Kim, K.D.; Zhao, J.; Auh, S.; Yang, X.; Du, P.; Tang, H.; Fu, Y.-X. Adaptive immune cells temper initial innateresponses. Nat. Med. 2007, 13, 1248–1252.