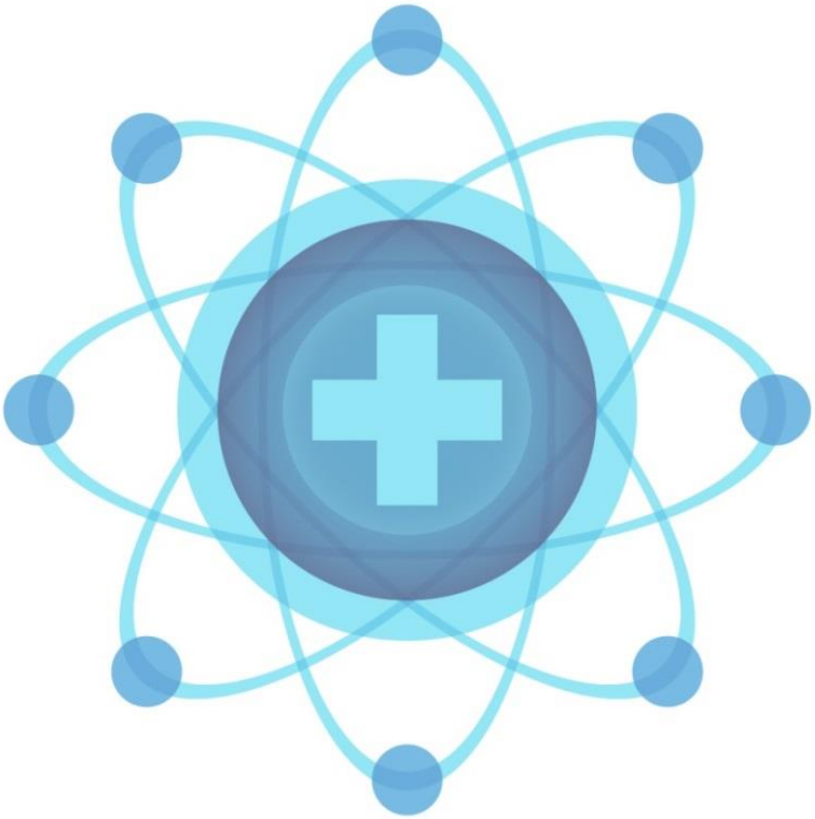

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THE ROLE OF TRANSFORMING GROWTH FACTOR- β1 IN THE DEVELOPMENT OF PROCESSES OF FIBROSIS IN THE HEART AND KIDNEY IN PATIENTS WITH DIABETES WITH CHRONIC HEART FAILURE.

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Abstract. The article evaluates the role of β1 transforming growth factor in the development of fibrotic processes in the heart and kidneys in chronic heart failure with diabetes and without it. It was also shown that these processes have a positive effect of complex treatment with the addition of type 2 glucose sodium co-transporter inhibitors - dapagliflozin.

Keywords: Chronic heart failure, diabetes, chronic kidney disease, dapagliflozin, β-transforming growth factor.

Actuality. Despite advances in research into the pathogenesis and course of chronic heart failure (CHF) and the widespread use of effective drugs in practice, it remains the final stage of the cardiovascular continuum. The disease is considered one of the important problems of medicine due to its high prevalence and development and ending with unpleasant consequences [14, 11].

In recent years, it has been noted that the high comorbidity in patients with CHF reduces their quality of life, leads to impaired social adaptation and increases the mortality rate. According to some data, the occurrence of comorbidity reaches 69% in 18-44-year-olds, 93% in 45-64-year-olds, and 98% in those over 65 [12].Its frequent occurrence and increasing number indicate the need to study this problem for Uzbekistan as well as for other countries [3].

In many cases, the comorbidity of CHF and chronic kidney disease (CKD) has a severe negative impact on life expectancy. These conditions are more and more often accompanied by diabetes mellitus (DM) or the development of serious complications on its basis. Therefore, it is important to study comorbid conditions, early diagnosis, effective treatment and prevention.

Long-term hypoxia and high concentration of uremic toxins in CHF have a strong cardiotoxic, vasotoxic and nephrotoxic effect. The nephrotoxic properties of uremic toxins are mainly related to their production in large quantities in the proximal segment of the nephron and their ability to accelerate the process of tubulointerstitial fibrosis, which is considered the main cause of intensive decline in kidney function. They activate nicotinamide-adenine-dinucleotide-phosphate-oxidase in the cells of proximal tubules and produce profibrotic cytokine β1 transforming growth factor (TGF-β1) with the participation of transcription factor NF-kappa-nucleus, causing local oxidative stress. It belongs to the group of multifocal cytokines and was first isolated from platelets in 1990. Normally, TGF-β1 is an important regulator of cell proliferation, differentiation, apoptosis, immune response, and extracellular matrix remodeling [5].

This cytokine, also plays an important role in the pathogenesis of the development of diabetic nephropathy in patients CHF with type 2 DM. It has been proven that the production of this cytokine increases in damaged kidneys. Various factors, in particular, hyperglycemia and angiotensin II increase TGF-β1 in podocytes and collagen synthesis in podocytes, resulting in thickening of the basement membrane and development of glomerulosclerosis [1, 15].

Based on the results of a large number of population and scientific studies, it can be said with confidence that there is a strong correlation between cardiorenal changes and cardiovascular diseases, including CHF. CKD develops in a number of cases as a result of CHF in the patient, and they have a reinforcing effect on each other. As a result, patient readmissions and deaths increase dramatically and financial costs increase. Therefore, the joint study of these problems and the search for new effective methods of treatment is one of the urgent problems of scientific and practical medicine [10, 4, 6].

In the countries of the world, including our Republic, the number of elderly people is increasing due to the increase in life expectancy. Naturally, in parallel with their increase in the society, an increase in the number of patients with CHF is also noted. In their treatment, comorbid conditions should be taken into account [7].

From this point of view, sodium glucose type 2 co-transporter (NGKT-2) selective inhibitors have been widely used in recent years as part of the standard treatment of CHF. A separate subanalysis of DAPA-HF was conducted in patients with the aim of evaluating the efficacy and safety of dapagliflozin, a representative of NGKT-2 selective inhibitors, depending on age [8].

The cardioprotective effect of dapagliflozin is due to reduction of body weight, blood pressure, albuminuria, slowing of vascular remodeling, improvement of capillary blood flow, improvement of endothelial function, reduction of secretion of pro-inflammatory cytokines, infiltration of vascular walls with macrophages, reduction of inflammatory-oxidative stress, and fibrosis processes in the heart, kidney and liver. It is manifested by slowing down [9].

Nephroprotective effect of NGKT-2 selective inhibitors is associated with intrarenal effect. It is associated with positive effects on tubules (reducing hypertrophy, and localized inflammation) and glomeruli (reducing hyperfiltration, glomerular hypertension, and albuminuria) [13].

In addition, the mechanism of the positive effect of this drug on markers of renal fibrosis and inflammatory cytokines, which have a negative effect on the condition of patients, especially when they are combined with type II DM, has not been studied separately [2].

The purpose of the study is to study the effect of TGF-β1 indicators and selective inhibitors of NGKT-2-dapagliflozin on the functional status of the heart and kidney and fibrosis processes in patients with chronic kidney disease developed on the basis of chronic heart failure in comorbidity with diabetes and without it.

Source and methods of research In the scientific work, 80 patients with chronic heart failure comorbidity with diabetes mellitus and without it, and developed chronic kidney disease S2 and S3a were observed. 45 of them (56.25%) were men and 35 (43.75%) were women. In order to solve the tasks, the scientific research work was carried out as follows.

The above 80 patients under observation were divided into the following groups: Group A- CHF +diabetes (40 patients), Group B- CHF +non-diabetes (40

patients) and both standard treatments (angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists , β-blockers, representative of mineralocorticoid receptor antagonists-veroshpiron, antiarrhythmics, anticoagulants and diuretics based on the instructions) patients who received drugs NGKT-2 inhibitor dapagliflozin (forsiga).

The diagnosis of CHF and its functional classes in the patients included in the study were determined based on their complaints, anamnesis, objective examination and laboratory-instrumental tests according to the criteria of the New York Heart Association (New York Heart Association, 1964).

In all cases, the diagnosis of diabetes was made after consultation with an endocrinologist and confirmed by appropriate laboratory tests, and patients diagnosed with type 2 diabetes with a disease duration of 3 or more years were included in the follow-up. During the follow-up, the patients were regularly monitored by an endocrinologist and hypoglycemic treatments were carried out according to their recommendation.Laboratory tests were performed before and after 3 months of treatment in all patients under observation. Also, calculation of glomerular filtration rate (GFR) from blood cystatin C level was determined according to the formula of Hoek et al. (2003).

All immunoenzyme and biochemical tests were carried out in the clinical-laboratory diagnostic department of the multidisciplinary clinic of the Tashkent Medical Academy on COBAC 6000 (Germany-Japan) equipment.

TGF-β1 in blood serum was determined by immunoenzymatic analysis using the reagents "Human TGF beta 1 ELISA Kit" (Bender MedSystems GmbH, Austria). The reagent set we used to detect TGF-β1 used a standard with a molecular weight of 26 kDa. Test sensitivity was 0.29 ng/ml.

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.

Research results. Taking into account the importance of determining TGF-β1 indicators and its correlation with heart and kidney functional status and inflammatory cytokines in the group of patients CHF with and without DM in our follow-up, we studied the reported cases. CHF II FC in patients with diabetes (group I A) interleukin (IL)-6 significantly (r=0.6, R<0.01) with TGF β1 and strongly positive with cystatin-S (r=0.86, R <0.001), strongly negative left atrial myocardial weight with GFR (r= -0.82, R<0.0001) and left ventricular ejection fraction (LVEF) (r=-0.8, R<0.0001) Average positive correlation (r=0.44, R<0.05) with left ventricular myocardium weight (LVMW) was noted. And in patients with CHF III FC diabetes (group I A), IL-6 with TGF β1 is high (r=0.7, R<0.001) and cystatin-S is strongly positive (r=0.9, R<0.001), Strong negative with GFR (r= -0.9, R<0.001) and left ventricular ejection fraction LVEF (r=-0.86, R<0.0001), significant positive with LVMW (r=0.6, R<0.05) a correlational relationship was established in table 1 below shows the results obtained.

Table 1 below compares post-treatment echocardiographic findings in CHF III FS patients.

Table 1. Indicators of cardiac intracardiac hemodynamics after treatment with various components in patients with diabetes mellitus of the III functional class of chronic heart failure.

№	References	Group A, CHF III FC with diabetes (n=20)		Group B, CHF III FC without diabetes (n=20)	
		Before treatment	After treatment	Before treatment	After treatment
1	Left ventricular end-systolic size (26-38 mm), mm	50,35±1,6	45,2±1,5*	46,9±1,5	42,4±1,3*
2	Left ventricular end-diastolic size (44-54	69.35±1,5	63,2±1,2**	65.3±1,2	60,2±1,1**

	mm), mm				
3	Left ventricular end-diastolic volume (88-145 ml), ml	203,9±7,9	178,4±6,8*	192,3±6,8	174,6±6,6
4	Left ventricular end systolic volume (45-68 ml), ml	112,3±9,1	89,6±8,1*	104,15±8,1	80,2±7,2*
5	Left ventricular ejection fraction, %	36,5±0,9	44,8±1,2***	41,7±1,3	47,2±1,2**
6	Left ventricular myocardial weight, g	246.75±6,2	230.2±5,5	240.9±5,5	221.2±5,3*
Note: * - the reliability of the difference between indicators before and after treatment: * - r<0.05., ** - r<0.01., *** - r<0.001					

Changes in left ventricular end-systolic size after the treatments were reliable in both groups of patients (R<0.05). Left ventricular end-diastolic size was 69.35±1.5mm before treatment and 63.2±1.2mm after treatment in the first group, 65.3±1.2mm and 60.2±1.1mm in the second group, respectively. When the changes in both groups were compared, highly reliable differences were noted (R<0.01). In the first group, left ventricular end-diastolic volume decreased from 203.9±7.9ml to 178.4±6.8ml (R<0.01). In the second group, the changes were not reliable (decrease from 192.3±6.8ml to 174.6±6.6ml, R>0.05). Left ventricular end-systolic volume decreased by 1.3 orders after the treatments in both groups and reliable differences were observed (R<0.05). The left ventricular ejection fraction increased from 36.5±0.9% to 44.8±1.2% in the first group after treatments, a highly reliable difference was noted (R<0.001). In the second group, it increased from 41.7±1.3% to 47.2±1.2% and a reliable difference was found (R<0.01). Left ventricular myocardium weight was reduced 1.07 times in patients receiving standard treatment+dapagliflozin (forsiga), but the changes were not reliable. In the second

main group of patients, the difference was reliable after treatment (from 240.9±5.5g to 221.2±5.3g, R<0.05).

So, if we conclude from the obtained results, the complex treatment containing dapagliflozin led to a positive change in cardiac hemodynamic indicators in patients, and consequently to stabilization of fibrosis processes. This was especially evident in patients with diabetes based on CHF II-III FC

Table 2 Comparative analysis of post-treatment TGF β1 levels in patients enrolled in the study.

№	References	Group A, CHF II FC with diabetes mellitus (n=20)		Group B, CHF II FC without diabetes (n=20)	
		Before treatment	After treatment	Before treatment	After treatment
1	**TGF β1**	4,77±0,3	3,5±0,27**	3,6±0,27	2,2±0,27***
		Group A, CHF III FC with diabetes mellitus (n=20)		Group B, CHF III FC without diabetes (n=20)	
2	**TGF β1**	7,4±0,3	4,6±0,4***	5,6±0,4	4,0±0,3**
Note: * - the reliability of the difference between indicators before and after treatment: * - r<0.05., ** - r<0.01., *** - r<0.001					

In group A CHF II FS diabetic patients, the TGF β1 values before treatment were 4.77±0.3 ng/ml and after 3.5±0.27 ng/ml, the difference between them was reliable (R<0, 01). In patients with CHF III FC diabetes, TGF β1 values decreased from 7.4 ±0.3 ng/ml to 4.6 ±0.4 ng/ml, 1.6 times, and a highly reliable difference was noted (R<0.001). Group B CHF II-III FC patients with and without diabetes had TGF β1 levels of 3.6 ± 0.27 ng/ml and 5.6 ± 0.4 ng/ml before treatment, respectively, and CHF II FC in patients after treatment it decreased 1.6 times to 2.2 ± 0.27 ng/ml and a highly reliable difference was observed (R<0.001). In patients with CHF III FC, it decreased 1.4 times to 4 ± 0.3 ng/ml and a reliable difference was found (R<0.01).

The reduction of TGF-β1 in the blood serum after the above-mentioned treatment means that the inflammation and fibrosis processes in the body of the patients involved in the study are reduced. These changes, in turn, have a positive effect on the functional state of the kidneys. We can see this in the improvement of GFR determined by cystatin-S in the observation patients.

Table 3. Comparative analysis of glomerular filtration rate (ml/min/1.73 m2) in patients enrolled in the study after different treatments.

№	References	Group A, CHF II FC with diabetes mellitus (n=20)		Group B, CHF II FC without diabetes (n=20)	
		Before treatment	After treatment	Before treatment	After treatment
1	**GFR**	56,75±2,2	68,4±2,4**	65,8±1,5	70,5±1,3
		Group A, CHF III FC with diabetes mellitus (n=20)		Group B, CHF III FC without diabetes (n=20)	
2	**GFR**	45,8±2,6	52,6±2,7	57,7±2,7	66,4±3,0*
Note: * - the reliability of the difference between indicators before and after treatment: * - r<0.05., ** - r<0.01., *** - r<0.001					

The glomerular filtration rate in group A CHF II FC diabetic patients was 56.75±2.2 ml/min/1.73m2 before treatment and 68.4±2.4 ml/min/1.73m2 after treatment, and was moderately reliable (R< 0.01) difference was noted. CHF III FC increased by 1.22 times from 45.8 ±2.6 ml/min/1.73m2 to 52.6 ±2.7 ml/min/1.73m2 after the treatments, and an unreliable difference was observed (R>0 .05). No reliable changes were noted in group B CHF II FC patients (R>0.05). In patients with CHF III FC, a reliable difference was found after treatments (57.7±2.7 ml/min/1.73m2 and 66.4±3.0 ml/min/1.73m2, respectively, R<0.05).

Summary. Our observations confirmed that positive dynamics of intracardiac hemodynamics, TGF β1 and GFR indicators were observed in both groups when dapagliflozin was added to complex treatments in patients with CHF type 2 DM and

without it. However, although these changes were more evident in the group without DM, reliable changes were also noted in most cases in patients with it.

Literature

1. Bobkova I.N., SHestakova M.V., SHCHukina A.A. Diabeticheskaya nefropatiya – fokus na povrezhdenie podocitov. Nefrologiya. 2015; 19(2): c. 33-43.

2. Novye vozmozhnosti meksikora v lechenii hronicheskij serdechnoj nedostatochnosti u bol'nyh s metabolicheskim sindromom / M. E. Stacenko [i dr.] // Rossijskij kardiologicheskij zhurnal. – 2010. – № 6 (86). – S. 28–33.

3. SHukurov R.T., Abdullaev T.A.. Gendernye razlichiya i komorbidnost' u bol'nyh s hronicheskoj serdechnoj nedostatochnost'yu. Kardiovaskulyarnaya terapiya i profilaktika. 2017; 16(6) s. 87-91.

4. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. Circulation. 2017;135(10):e146-e603. doi:10.1161/CIR.0000000000000485.

5. Bottinger E.P., Bitzer M. TGF-p signaling in renal disease // J. Am. Soc. Nephrol. — 2002. — Vol. 13. — P. 2600-2610.

6. Lam CSP, Chandramouli C, Ahooja V, Verma S. SGLT-2 Inhibitors in Heart Failure: Current Management, Unmet Needs, and Therapeutic Prospects. J Am Heart Assoc. 2019;8(20):e013389. doi:10.1161/JAHA.119.013389.

7. Li H, Hastings MH, Rhee J, et al. Targeting Age-Related Pathways in Heart Failure. CircRes. 2020;126(4):533-51. doi:10.1161/CIRCRESAHA.119.315889.

8. Martinez FA, Serenelli M, Nicolau JC, et al. Efficacy and Safety of Dapagliflozin in Heart Failure With Reduced Ejection Fraction According to Age: Insights From DAPA-HF. Circulation. 2020;141(2):100-111. doi:10.1161/CIRCULATIONAHA.119.044133.

9. Petrykiv S., Sjöström C.D., Greasley P.J. et al. Differential effects of dapagliflozin on cardiovascular risk factors at varying degrees of renal function // Clin. J. Am. Soc. Nephrol. 2017. Vol. 12. № 5. P. 751–759.

10. Seferović PM, Petrie MC, Filippatos GS, et al. Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018;20(5):853-72. doi:10.1002/ejhf.1170.

11. Shah KS, Xu H, Matsouaka RA, Bhatt DL, Heidenreich PA, Hernandez AF et al. Heart Failure with Preserved, Borderline, and Reduced Ejection Fraction. Journal of the American College of Cardiology. 2017;70(20):2476–86. DOI: 10.1016/j.jacc.2017.08.074.

12. Silverberg DS. J Am Coll Cardiol 2000. – Том 35, №7. – P.1737-44., Dickson V.V., Buck H., Riegel B. A qualitative meta-analysis of heart failure self-care practices among individuals with multiple comorbid conditions // J. of Cardiac Failure. - 2011. -Vol. 17, № 5. - P. 413-419.

13. Škrtić M., Cherney D.Z. Sodium-glucose cotransporter-2 inhibition and the potential for renal protection in diabetic nephropathy // Curr. Opin. Nephrol. Hypertens. 2015. Vol. 24. № 1. P. 96–103.

14. Tsao CW, Lyass A, Enserro D, Larson MG, Ho JE, Kizer JR et al. Temporal Trends in the Incidence of and Mortality Associated with Heart Failure with Preserved and Reduced Ejection Fraction. JACC: Heart Failure. 2018;6(8):678–85. DOI: 10.1016/j.jchf.2018.03.006.

15. Wolf G, Chen S, Ziyadeh FN. From the periphery of glomerular capillary wall toward the center of disease: podocyte injury comes of age in diabetic nephropathy. *Diabetes.* 2005; 54(6): p. 1626-1634.