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EFFECT OF DAPAGLIFLOZIN ON RENAL FIBROSIS IN CHRONIC HEART FAILURE WITH ANEMIA

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ABSTRACT: In this scientific research, the effect of standard treatments containing gliflozin, i.e. glucose sodium cotransporter type 2 inhibitor dapagliflozin-forsi, on kidney function, in particular, on glomerular filtration rate and collagen Ⅳ indicators in urine, in patients with chronic heart failure who have been diagnosed with anemia. A significant decrease in the amount of collagen Ⅳ in the urine after the first month of treatment in the group of patients who received dapagliflozin confirmed the effective effect of the drug on the fibrotic processes in the kidney.

KEYWORDS: Chronic heart failure, dapagliflozin, glomerular filtration rate, collagen IV.

INTRODUCTION

CHF is one of the important problems of modern medicine, and with increasing age, the prevalence of this serious complication is increasing among older people, and its main causes are arterial hypertension (AG) and ischemic heart disease (IHD). [23, 4, 18,]. In recent years, special attention has been paid to the association of CHF with anemia. According to information from various scientific sources, the prevalence of anemia is determined from 4% to 71% of patients with CHF, depending on its diagnostic criteria [17, 12]. According to a number of authors, the general factors predicting the course of CHF include the patient's age, hemoglobin index, the presence of heart defects, the amount of sodium in the blood serum, and impaired renal function. [3, 4, 9, 24]. In recent years, the use of glucose-sodium cotransporter 2 inhibitors (GNKT2i) has been shown to be effective in patients with low left ventricular ejection fraction (LVEF) [21]. Currently, dapagliflozin, empagliflozin, canagliflozin and other drugs belonging to this group have been created [22].

Their representative dapagliflozin (Forsiga) is effective and safe in patients with low left ventricular ejection fraction (LVEF), regardless of glycosylated hemoglobin levels [21].

The observations showed that dapagliflozin was effective regardless of whether patients received standard combination therapy or not. No changes related to renal impairment were observed in the patients. However, renal dysfunction was observed when diuretics, 50% more than the target dose of MKRA or AAFI or ARA, BAB and MKRA were taken [8].

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THE PURPOSE OF THE RESEARCH

Comparative study of the nephroprotective effect of GNKT2i, i.e. gliflozin dapagliflozin, in patients with CHF anemia.

RESEARCH MATERIALS AND METHODS

This scientific research work was conducted in 2021 and 2022 in the cardiology and cardiorehabilitation departments of the multidisciplinary clinic of the Tashkent Medical Academy in patients with developed CHF based on YuIK and GK. Based on the goals and tasks set before us, the scientific research work was carried out as follows.

120 patients with CHF Ⅱ and Ⅲ FC were included in the follow-up and divided into two groups. The first group was diagnosed with CHF Ⅱ and Ⅲ FC iron deficiency anemia and received glucose-sodium cotransporter 2 inhibitor (gliflozins) dapagliflozin-forsi as part of complex standard treatment, and the second group was diagnosed with CHF Ⅱ and Ⅲ FC iron deficiency anemia and received complex standard treatment patients organized. Both groups of patients were prescribed iron (III) sucrose intravenously.

The first group consisted of 80 patients and their average age was 65.1±1.2 years, 22 (41.5%) men and 31 (58.5%) women. This group, in turn, was divided into two subgroups based on the FC of CHF.

The first subgroup consisted of 40 patients with II FC of CHF, their mean age was 65.2±1.4 years, 24 (60%) men and 16 (40%) women. 26 (65) had myocardial infarction (MI), 11 (27.5) had coronary artery bypass grafting (ACS) or stenting, 8 (20) had obesity, type II diabetes) - 4 (10%) people.

The second subgroup consisted of 40 patients with III FC of CHF. Their average age was 65.1±1.6 years, men were 19 (47.5%) and women were 21 (52.5%). 21 (52.5%) had MI, 9 (22.5%) had coronary artery disease or stenting, 11 (27.5%) were obese, and 6 (15%) had QD II.

The second group consisted of 40 patients, their average age was 66.3±2.0, 20 (50%) men and 20 (50%) women. This group, in turn, was divided into two subgroups based on the FC of CHF.

The first subgroup consisted of 20 patients with II FC of CHF, their average age was 68.4±2.1 years, 10 (50%) men and 10 (50%) women. 11 (55%) had MI, 6 (11.3%) had ACS or stenting, 16 (30.1%) were obese, and 4 (7.5%) had QD II.

The second subgroup consisted of 20 patients with III FC of CHF. Their average age was 64.4±1.2 years, with 10 (50%) males and 10 (50%) females. 17 (85%) had MI, 8 (40%) had coronary artery disease or stenting, 16 (30.1%) were obese, and 10 (50%) had QD II.

The diagnosis of CHF and its FC in patients is based on the complaints of observers, the study of medical history, objective examination and laboratory-instrumental examinations in accordance with the "Recommendations for the diagnosis and treatment of acute and chronic heart failure" updated by the European Association of Cardiology in 2021 and the New York Society of Cardiology (New York It was determined according to the criteria of Heart Association, 1964).

In follow-up patients, laboratory-instrumental and functional examinations were performed 1-3 days after admission to the hospital, and the next examination was performed after 1 month of

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treatment. Also, glomerular filtration rate in patients was calculated using the formula EPI (CKD-EPI creatinine equation).

The level of type IV collagen in urine was determined as follows. A mid-morning portion of urine was aseptically collected in a sterile container. After the sample was centrifuged, solid particles were removed. It should be tested immediately or eaten and stored at ≤ -20°C. The samples were brought to room temperature before testing. (refreezing and thawing should be avoided). To dilute the standard, it was dissolved in 1.0 ml of buffer, kept at room temperature for 10 minutes and mixed carefully. The concentration of the stock solution is 500 ng/ml. 7 test tubes containing 0.5 ml of standard diluent and the concentration shown below were prepared. The mixer tips were mixed thoroughly before further addition. The standard was prepared by diluting the following 7 points: 500 ng/ml, 250 ng/ml, 125 ng/ml, 62.5 ng/ml, 31.2 ng/ml, 15.6 ng/ml, 7.8 ng/ml at a final concentration of 0 ng/ml of the standard in the Eppendorf tube should be.

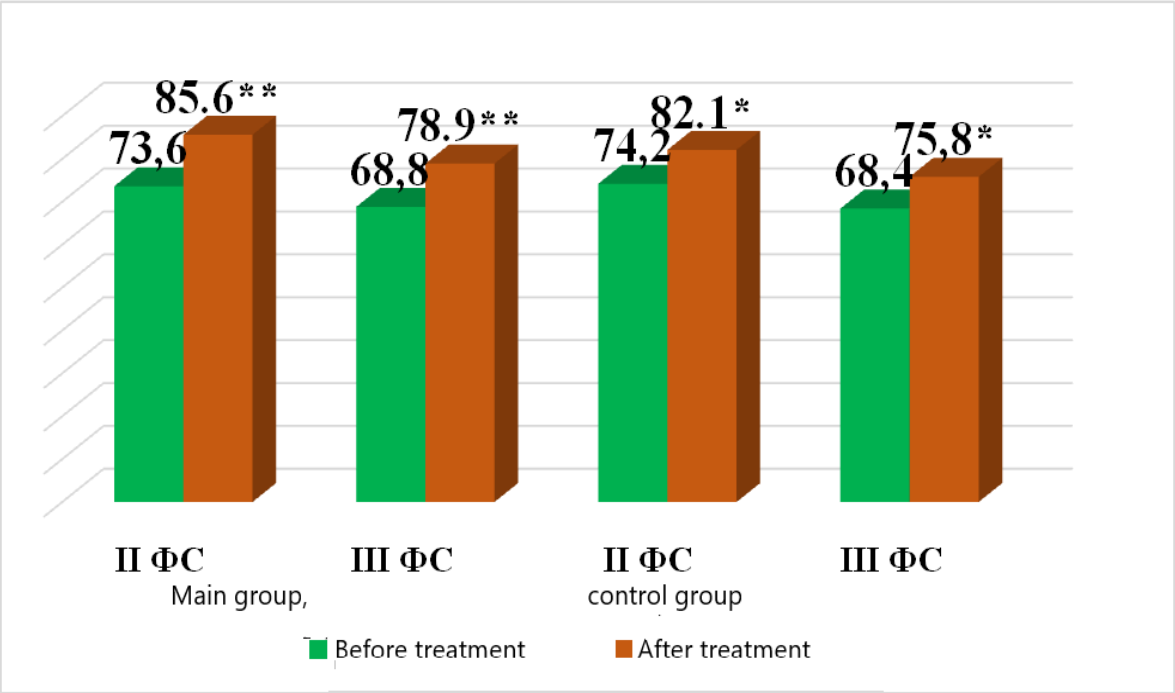
The range of measurable indicators is 7.8-500 ng/ml. standards used were included in the calibration curve at concentrations of 500 ng/ml, 250 ng/ml, 125 ng/ml, 62.5 ng/ml, 31.2 ng/ml, 15.6 ng/ml, 7.8 ng/ml.

RESEARCH RESULTS AND DISCUSSION

Initially, in the first month of treatment, the functional state of the kidneys and collagen IV indicators in the urine were evaluated using CFT. Figure 1 below presents a comparative analysis of CFT before and after treatments.

1-Table

Comparative analysis of glomerular filtration rate (ml/min/1.73m2) in patients enrolled in the study before and after the first month of treatment with different components.



Explanation; * - differences are significant compared to pre-treatment and post-treatment indicators (*-P <0,05, ** - P <0,01, * - P<0,001)**

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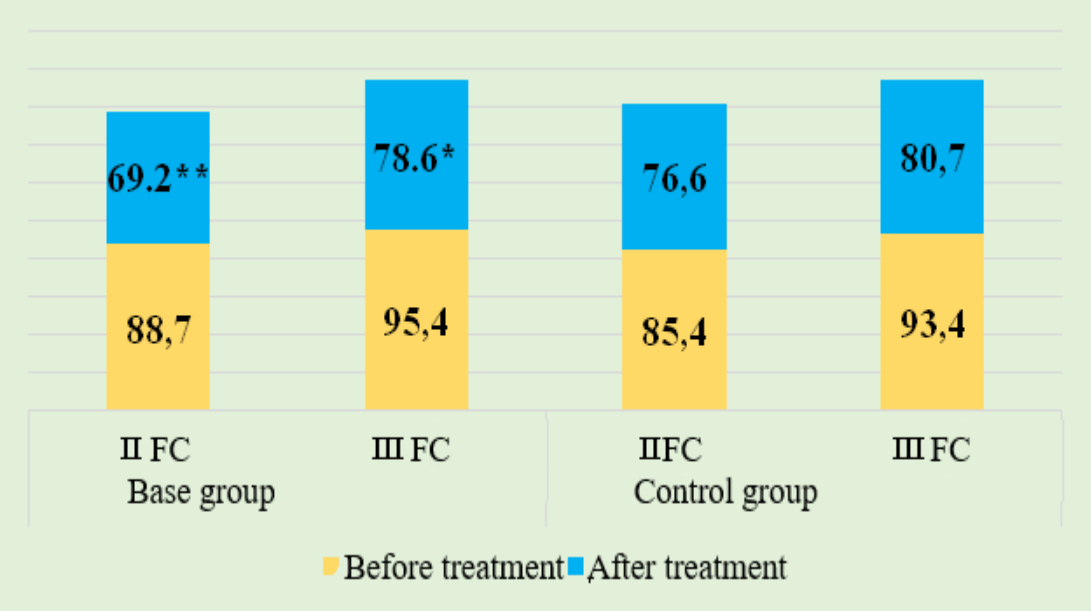
Glomerular filtration rate increased 1.16 times to 73.6±2.8 ml/min/1.73m2 before treatment and 85.6±3.1ml/min/1.73m2 in the main group of patients with CHF Ⅱ FC and moderately reliable (R< 0.01) difference was detected. And in CHF Ⅲ FC, before and after the treatments, respectively, from 68.8±2.3 ml/min/1.73m2 to 78.9±2.5 ml/min/1.73m2, an average reliable difference was observed (R<0.01). CHF Ⅱ of the control group improved 1.1 times from 74.2±2.5 to 82.1±2.6 ml/min/1.73m2 after treatments and reliable changes were noted (R<0.05). A reliable difference after treatment was also found in patients with CHF Ⅲ FC (68.4±2.5 ml/min/1.73m2 and 75.8±2.4 ml/min/1.73m2, respectively, R<0.05). The analysis showed a highly reliable increase in glomerular filtration rate after one month of treatment in the group that received dapagliflozin (forsiga) and intravenous iron on the basis of the main, that is, standard treatment. Significant changes were also observed in the control group (R<0.01 and R<0.05, respectively) but were not significant.

Determination of collagen Ⅳ in the urine of patients is one of the markers indicating the level of fibrosis processes in the kidneys. Figure 2 below shows a comparative analysis of collagen Ⅳ values in the first month after treatment.

2-Table

Urine collagen Ⅳ indicators (µg/l) in patients involved in the study before and after complex medical treatments with different components



Explanation; * - differences are significant compared to pre-treatment and post-treatment indicators (*-P <0,05, ** - P <0,01, * - P<0,001)**

After the treatment procedures, collagen Ⅳ levels in the main group of patients with FC II who received dapagliflozin (forsiga) based on the standard treatment of CHF were 88.7±5.2 µg/l before the treatment and 69.2±4.2 µg/l after the treatment, and it decreased by 1.3 times, and a high reliable difference was recorded. (p<0.01). In patients with CHF Ⅲ FC, its content decreased by 1.2 times to 95.4±5.6 µg/l and 78.6±4.8 µg/l, respectively, before and after treatment (p<0.05).

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The values of collagen Ⅳ in urine in the control group of patients with CHF Ⅱ FC before and after the treatments were 85.4±5.4 µg/L to 76.6±4.8 µg/L, and the values in the patients with CHF Ⅲ FS were 93.4±4.6 µg/L and 80.7± 80.7 µg/L before and after the treatment, respectively. It was 5.2 µg/l and decreased by 1.1 times in both groups, but the differences were not reliable (p>0.05). The main group confirms that dapagliflozin (forsiga) in the standard treatment is effective compared to AAFIs in renal fibrosis processes in patients with a significant decrease in urinary collagen Ⅳ after the first month of treatment.

The obtained results showed that in the main group receiving dapagliflozin (forsiga) on the basis of standard treatment, CFT indicators changed in a highly reliable positive direction in the first month. This is not related to hyperfiltration, but to the positive effect of glucose sodium cotransporter type 2 inhibitors on systemic inflammation and tubulointerstitial sclerosis processes, as well as on hemodynamic changes. After treatment, CFT approaches the primary indicators, on the contrary, it indicates the stabilization of the process, showing the renoprotective effect of the drug. [14, 1, 5, 11, 6].

It is known that CFT is partially controlled by tubuloglomerular reconnection. An increase in sodium concentration in the distal tubules increases the release of adenosine from the dense patch. This, in turn, causes narrowing of the arterioles of the afferent balls and a decrease in CFT. An increase in sodium reabsorption in the proximal tubules reduces the concentration of sodium chloride in the dense macula. This causes disruption of tubular-glomerular reconnection and dilatation of afferent arterioles. In parallel, RAAT is activated, and as a result, narrowing of the leading arteries is observed. The listed changes together lead to an increase in CFT in each nephron. As a result, glomerular hyperfiltration and hypertension are observed in patients, which lead to worsening renal dysfunction [2, 16]. Drugs of the GNKT2i group have a positive effect on CFT by blocking glucose and sodium reabsorption in the proximal tubules, the negative effects listed above [19, 16, 7, 20].

In addition to numerous data published in the literature in recent years, it is considered that GNKT2i alleviates metabolic stress, normalizes oxygenation in the renal cortex, reduces tubulointerstitial fibrosis, and reduces hypoxic conditions around the proximal tubules [15]. This is partly due to the fact that this group of preparations improves the hematological condition and has a positive effect on the oxygenation of the body [10, 13, 15].

CONCLUSION

The decrease in the urinary excretion of collagen Ⅳ in the patients taking dapagliflozin (forsiga) involved in the study can be estimated to be related to the drug's effect on the proximal tubules of the kidney and stabilization of fibrosis processes. Because in numerous data, the process of tubulointerstitial fibrosis begins precisely in the area of proximal tubules.

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