PSYCHOLOGY AND EDUCATION (2021) ISSN: 0033-3077 Volume: 58(3): Pages: 1291-1301
Article Received: 13th September, 2020; Article Revised: 25th January, 2021; Article Accepted: 12th February, 2021

Dynamics of Renal Fibrosis Markers on the Basis of Complex Treatment in Chronic Heart Failure with Anemia

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Abstract. Renal fibrosis markers were evaluated in dynamics to study specific changes in the kidneys of patients with different hemodynamic types and functional classes of chronic heart failure with anemia and to evaluate the effectiveness of complex treatment. The renal fibrosis marker TGF-β_1 in the blood was 2591.0 ± 108.4 and 755.0 ± 18.87 pg / ml, respectively, in the absence of chronic heart failure and anemia ($p<0.001$). This was indicative of a fibrosis process occurring in the kidney. After complex treatment with iron supplements, the TGF-β_1 index decreased by 2.25 times (p (0.001), the clinical condition, quality of life and endurance to physical activity changed significantly positively.

Key words:chronic heart failure, chronic kidney disease, renal dysfunction, fibrosis markers, anemia, anemia, hemoglobin, iron in the blood, hemodynamic types.

Introdaction. Experts from the World Health Organization describe the growing prevalence of chronic diseases as a global epidemic of the 21st century (27). The specific features of modern treatment and diagnostic processes for chronic heart failure (CHF), which are among them, require the consideration of a combination of several pathological conditions in the patient, i.e. comorbidity (28).

High comorbidity leads to increased mortality from chronic diseases, decreased quality of life, and impaired social adjustment (16). Numerous observations have confirmed that cardiovascular disease and its severe complications are one of the leading causes of death among the population worldwide, including in Uzbekistan (9, 29). Comorbidity is one of the leading factors in this.

The fact that a number of studies have shown a high risk of death in a patient with chronic comorbidities also indicates the relevance of the topic (26, 14). Furthermore, from a social point of view, comorbidity leads to a decrease in patients 'quality of life and limited self-care, as well as aggravating the consequences of the disease, leading to disability, and dramatically increasing the risk of hospitalization (32).

In recent years, special attention has been paid to factors that negatively affect the quality and duration of life of patients with CHF, and among them, anemia is one of the leading ones. In developed countries, anemia is observed in 10–55% of patients with CHF, a rate that corresponds to the functional class of the disease (FCD) and occurs in up to 80% in its IV FCD (7; 14; 31; 3). In recent years, it has been viewed as an independent risk factor that negatively affects the course of the underlying disease and its consequences (21; 14). There are different views on the course and pathogenesis of anemia in patients with CHF, which also requires an in-depth study of the problem. The peculiarities of the course of the disease, the shortening of life expectancy of patients and the doubling of mortality compared to those who do not have it, confirm that early diagnosis, effective treatment and prevention of the pathological process is one of the current problems in applied medicine.

Also, one of the important issues facing scientific research on this issue is the early and interrelated detection of renal dysfunction in patients with

CHF and anemia. This is because the addition of renal changes in patients with CHF comorbidities with anemia not only leads to hospitalization and recurrence, but also worsens their quality of life and dramatically increases mortality. Prolonged latent renal dysfunction in them exacerbates the problem (15; 26). In a number of cases, including CHF, the clinical manifestations of chronic kidney disease (CKD) gradually worsen the course of the underlying disease over several years (18; 23). Therefore, one of the most important problems of modern medicine is the early detection of renal dysfunction in comorbid conditions with anemia, the development of alternative methods of effective influence on the process, the creation of measures aimed at improving the quality of life and renal function of patients.

The purpose of the study. Evaluation of the dynamics of renal fibrosis markers on the basis of complex treatment of patients with anemia and anemia CHF.

Material and methods. The 110 patients with CHF involved in the study were divided into 2 groups (70 of whom were anemic and 40 of whom were without anemic) and underwent excellent clinical and laboratory examinations. The biochemical tests performed and the methods used are given in the first table.

Table 1
Methods used in biochemical examination of blood

№	Names of inspections	Verification method
1	Iron	Colorimetric
2	Ferritin	Colorimetric
3	Transferrin	immunoenzyme assay
4	β_1-transforming growth factor	immunoenzyme assay
5	Cystatin S	Immunoturbidimetric
6	Potassium	Turbodimetric
7	Sodium	Turbodimetric

This group included patients with existing FCD II and III FCD, who formed age-appropriate indicators. Their ages ranged from 50 to 70 years, with an average of 64.9 ± 4.9. All patients underwent outpatient follow-up after treatment in a hospital setting and were divided into two main and control groups. As noted above, the main group consisted of 70 patients with CHF anemia and 40 patients who had no CHF anemia. In all of them, the ferrokinetic parameters in the blood and the functional status of the kidney, as well as its fibrosis markers, compared in the first table, were studied comparatively.

In the main group of patients treated in the hospital on the basis of standard treatment CHF (angiotensin-converting enzyme inhibitors or angiotensin 2 receptor antagonists, b-blockers, diuretics, cardiac glycosides and antiarrhythmic drugs as an antiaremic complex (saccharin III complex) venofer) 200 mg intravenously. The total dose of the drug administered to eliminate iron deficiency, using a special formula adopted for the treatment of venofer [total iron deficiency = body weight, kg x (150 - patient hemoglobin index Hb, g / l) x 0.24 + 500 mg] calculated.

Research results and discussion. In 110 of them, ferrokinetic parameters in the blood and functional status of the kidney and its fibrosis markers were compared comparatively. The results of the analysis are presented in Table 2**.**

Table 2
Ferrokinetic and renal functional status and its indicators of fibrosis markers in patients with chronic heart failure, anemia and without anemia

№	Indicators	Treatment steps	The main group of patients with chronic heart failure anemia n = 70	Patients in the control group with chronic heart failure without anemia n = 40
1	Hemoglobin, g / l	Before	101.4±0.9	136.5±1.1
		After	134.4±1.0	134.4±0.8
2	Hematocrit,%	Before	37.3±0.62	40.9±0.37
		After	40.1±0.62	40.1±0.1
3	Erythrocytes, x1012l	Before	3.6±0.04	4.3±0.04
		After	4.1±0.1	4.2±0.2
4	ESR, mm / h	Before	15.7±1.09	12.5±1.07
		After	11.2±1.2	10.8±1.2
5	Glucose, mmol / l	Before	5.1±0.32	5.5±0.08
		After	5.0±0.2	5.3±0.02
6	Serum iron, mmol / l	Before	7.9±0.2	23.3±0.4
		After	39.1±1.1	26.7±0.6
7	Ferritin, mg / l	Before	82.2±2.9	349.8±9.9
		After	284.6±8.3	351.5±9.0
8	Transferrin, mg / l	Before	4.9±0.1	3.8±0.1
		After	2.9±0.1	3.5±0.1
9	Transfer saturation,%	Before	16.2±3.2	26.3±8.6
		After	25.2±4.1	25.8±7.2
10	TGF-β_1, pg / ml	Before	2591.0±108.4	755.0±18.87
		After	1150.0±38.9	670.6±16.1
11	Cystatin S, mg / l	Before	1.43±0.06	0.83±0.01
		After	0.9±0.01	0.81±0.01
12	Ball filtration rate ml / min / 1.73m2	Before	55.2±1.6	92.3±1.3
		After	84.1±0.8	95.6±1.3

Hemoglobin levels in the main group of patients before treatment were 101.4 ± 0.9 g / l. In the control group, this value was 136.5 ± 1.0 g / l. In the main group of patients, the hemoglobin index was significantly lower than in the control group by 25.8% ($p < 0.01$). A reliable negative ($r = -0.238$, $p < 0.05$) correlation between hemoglobin and glomerular filtration was also found in cases of chronic heart failure with anemia. This confirms that a decrease in hemoglobin levels in CHF leads to a decrease in the rate of glomerular filtration.

Based on the complex treatment, the hemoglobin index in the main group of patients was 134.4 ± 1.02 g / l, a reliable increase compared to the initial value ($p < 0.001$) (Fig. 1).

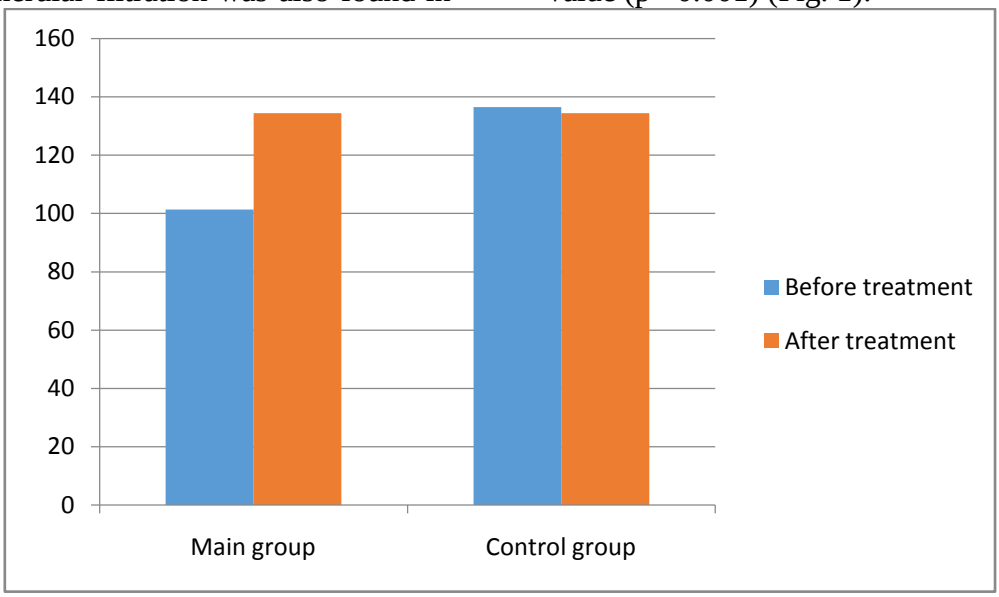

Figure 1. Pre- and post-treatment indicators of hemoglobin levels in patients with chronic heart failure, anemia and without anemia.

It is known that iron plays an important role in metabolic processes in the body, especially in the delivery of oxygen to the tissues. Hemoglobin, analyzed above, along with myoglobin, is one of the major iron-containing proteins. It is known that CHF is often accompanied by iron deficiency anemia. In this context, the determination of iron levels in the blood is of great practical importance in its treatment. In a comparative study of serum iron levels in the patients in our follow-up, it was 7.9 ± 0.2 mmol / l and 39.1 ± 1.1 mmol / l, respectively, before and after treatment in the main group with CHF anemia, with significant differences ($p < 0.001$) and baseline increased by 20.5% compared to. In the control group, ie in the CHF anemic group, these numbers were 23.3 ± 0.4 mmol / l and 26.7 ± 0.6 mmol / l, respectively.

In the main group of patients, the level of iron in the blood was found to be less reliable ($p < 0.001$) than in the control group. After complex treatments, it was noted that in the main group of patients its value was 4.9 times higher than reliable ($p < 0.001$) (Fig. 2).

A reliable positive ($r = 0.485$, $p < 0.014$) correlation between iron and hemoglobin was also found in patients with CHF anemia.

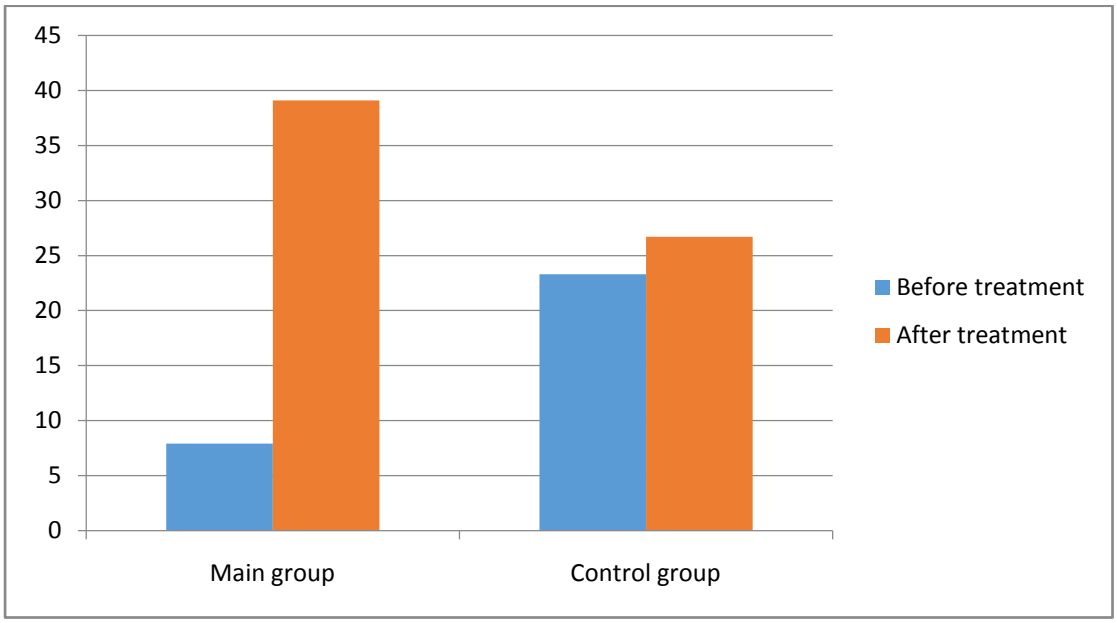

Figure 2. Pre- and post-serum iron indications in patients with chronic heart failure anemia and without anemia.

This CHF also confirms a decrease in hemoglobin levels in association with a decrease in serum iron, which has been proven in numerous observations.

One of the main ferrokinetic parameters in blood serum is ferritin, a semi-crystalline structure composed of Fe + 3 hydrate and apoferritin. Ferritin circulates in the blood and in physiological conditions is directly related to the amount of iron reserves in the body. An increase in its amount in the blood serum by 1mk / l corresponds to an increase in iron reserves of 8-10 mg. Therefore, ferritin levels in the blood are used to determine the body's iron reserves. In this context, a comparative study of serum ferritin levels in the follow-up patients was 82.2 ± 2.9 mg / l before and 284.6 ± 8.3 mg / l in the main group of patients with CHF anemia, and the values differed reliably ($p < 0.001$). . In the control group, where CHF was anemic, these values were 349.8 ± 9.9 mg / l and 351.5 ± 9.0 mg / l, respectively (Figure 3).

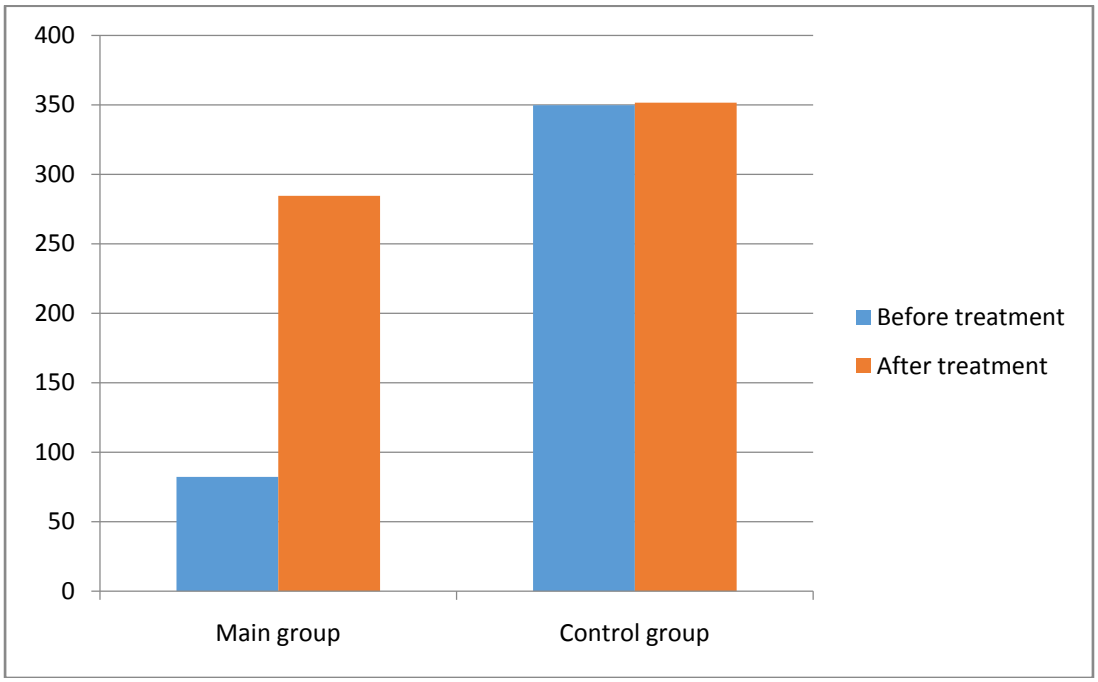

Figure 3. Pre- and post-treatment indications for serum ferritin in patients with chronic heart failure, anemia, and without anemia.

Serum ferritin levels in patients in the main group showed a high reliable difference compared to those in the control group ($p < 0.001$) and no reliable difference was found between them after treatment with intravenous venofer on the basis of complex treatments.

Another ferrokinetic indicator of blood is transferrin, which belongs to the group of metal-binding and transporting proteins. Transferrin is mainly synthesized from the liver and about half is in the bloodstream in the veins and the rest is out of it. Transferrin forms an easily dissociated compound with iron and converts it into a non-toxic form. In this case, it allows the iron reserves to be easily distributed in the body. Therefore, a comparative study of transferrin levels in the serum of patients with CHF anemia and without it is of practical importance. At the same time, in the group with primary anemia, its values before and after the treatment were 4.9 ± 0.1 mg / l and 2.9 ± 0.1 mg / l, respectively, and the values between them differed from each other reliably ($p<0.001$). These values were 3.8 ± 0.1 and 3.5 ± 0.1 mg / l, respectively, in the control group (Figure 4).

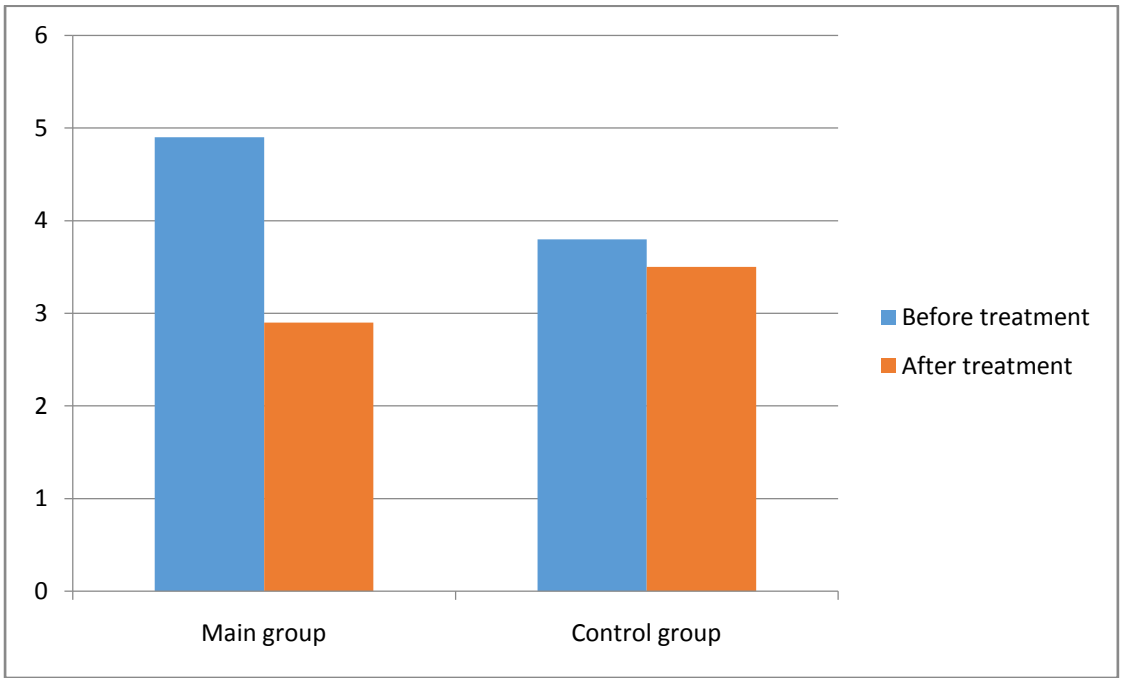

Figure 4. Pre- and post-treatment indications for serum transferrin in patients with chronic anemia and without anemia.

In the main group of patients, serum transferrin levels were reliably different from the control group ($p<0.001$). After complex treatments with the addition of iron, the difference between them sharply decreased.

In the next phase of the study, CHF studied the functional status of the kidney in patients with anemia and anemia and some of its fibrosis markers before and after complex treatments with the addition of iron - venofer (in the main group).

The importance of determining the amount of TGF-β_1 in the blood, which is a marker of tubulointerstitial fibrosis processes in the kidney, has been proven in a number of studies. It is known that this cytokine plays an important role in the processes of sclerotic damage of the renal tubules and the surrounding interstitial tissue. Therefore, its blood parameters were studied in patients with CHF anemia and anemia. They differed reliably ($p<0.001$) from each other in these groups with 2591.0 ± 108.4 and 755.0 ± 18.87 pg / ml, respectively.

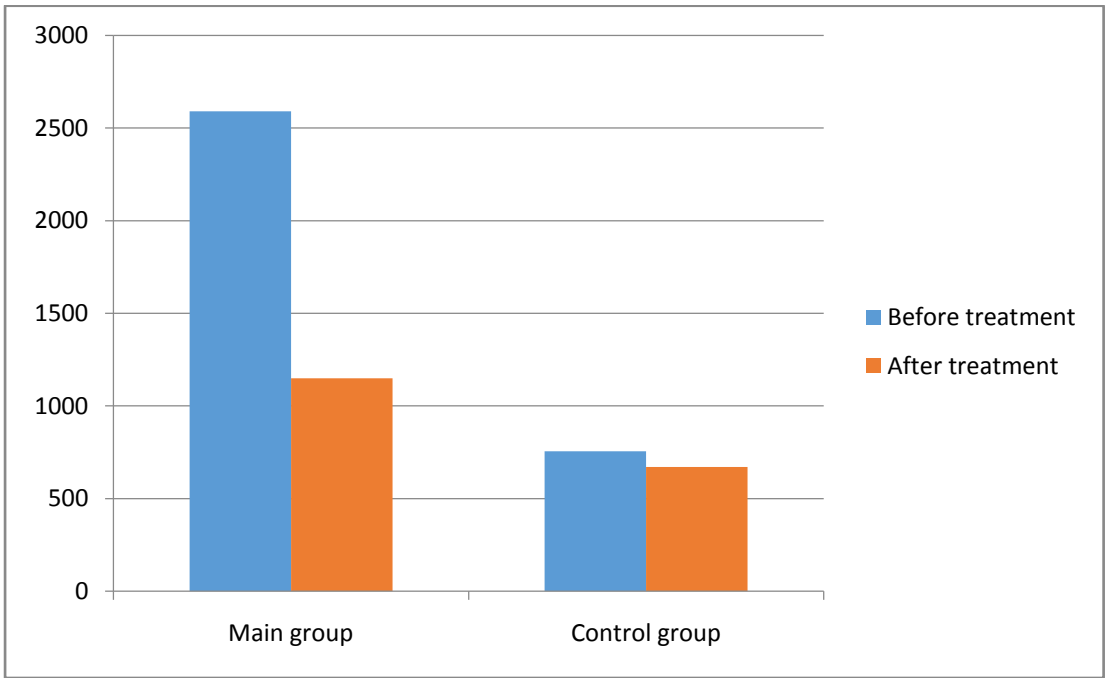

Figure 5. Preoperative and post-treatment serum TGF-b1 in patients with chronic heart failure, anemia, and without anemia.

After complex treatments with the addition of iron, the values decreased to 1150.0 ± 38.9 pg / ml, which is 2.25 times less reliable than the primary ($p<0.001$) (Fig. 5). Also, in the main group of patients, the negative correlation between TGF-β_1 and hemoglobin was reliable ($R<0.05$) $r = -0.24$. This indicates an increase in TGF-β_1, a decrease in hemoglobin in the blood, or vice versa, an increase in hemoglobin.

Furthermore, the identified correlation between TGF-β_1 and glomerular filtration in this group confirms an increase in renal fibrosis markers when CHF occurs with anemia, leading to a decrease in glomerular filtration ($r = -0.1$ and $p<0.05$).

Complex treatments with the addition of iron lead to a decrease in TGF-β_1, an increase in hemoglobin and a positive shift in the rate of glomerular filtration.

Furthermore, a reliable ($p<0.05$) positive correlation ($r = 0.7$) was noted between TGF-β_1 and cystatin-S in this group.

It is known that an increase in cystatin-S in the blood indicates a decrease in glomerular filtration. Balls with TGF-β_1 indeed the existing reliable ($p<0.05$) negative relationship ($r = -0.74$) between filtration confirms this.

In the next step, we studied the marker cystatin-S, which allows us to assess the functional status of the kidneys, and the filtration of the balls detected using it. In recent years, extensive use of cystatin-C has been recommended in the assessment of renal functional status. It is a weight-independent, age-independent polypeptide unlike creatine. Therefore, it is advisable to use it in assessing the functional status of the kidneys. Cystatin-C was 1.43 ± 0.06 mg / l in the main group of patients in our preoperative follow-up. In the control group, this value was 0.83 ± 0.01 mg / l. Cystatin-C was reported to be 1.7 times higher in the baseline group than in the control group. After complex treatments, these values were 0.6 ± 0.01 mg / l in the main group and 0.81 ± 0.01 mg / l in the control group, respectively (Figure 6).

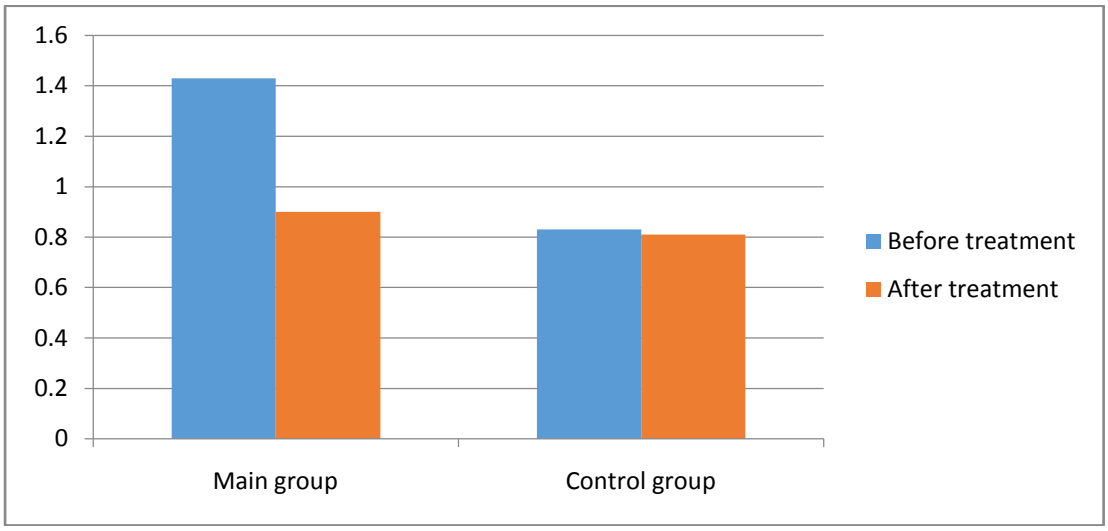

Figure 6. Preoperative and post-treatment indications for serum cystatin-C in patients with chronic heart failure and without anemia.

At the same time, a reliable decrease in cystatin-C ($p<0.01$) was observed in patients with CHF anemia. No reliable changes were detected in the control group ($p>0.05$).

An increase in serum cystatin-S has been shown to lead to a decrease in glomerular filtration ($r = -0.9$, $p<0.001$), which has been confirmed by our observations.

The filtration rate of 1.73 m2 body-level balls detected using cystatin-C was also found to be different in both groups of patients monitored before complex treatments. In the main group of patients with CHF anemia, this value was 65.2 ± 1.6 ml / min, in control, ie 92.3 ± 1.3 ml / min in cases where anemia was not detected, the values differed reliably ($R<0.001$).

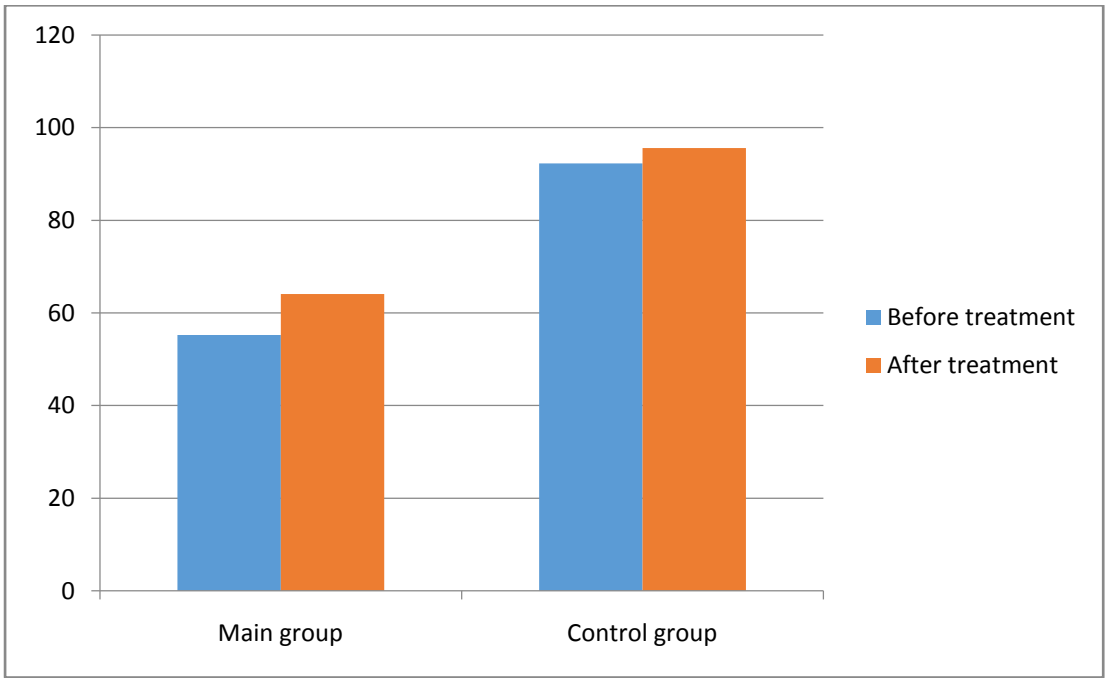

Figure 7. Indications for ball filtration rate before and after treatment in patients with chronic heart failure, anemia andwithout anemia.

After the procedures, it was found that in the main group, this figure increased by 8.2% compared to the original. In the control group, however, the filtration rates of the balls before and after treatment did not differ significantly from each other (Fig. 7).

As mentioned above, the existence of a correlation between TGF-β_1 and cystatin-S ($r = -0.7$, $r = -0.6$, $r = -0.9$, $R<0.05$) was confirmed.

The analysis showed that fibrous processes in the kidneys intensify when CHF passes with anemia. This was confirmed by the existing reliable correlation between hemoglobin and TGF-11, as well as a reliable low rate of cystatin-C-induced glomerular filtration rate in patients with anemia compared with those without anemia. Consequently, the addition of anemia in CHF accelerates fibrous processes in the kidney. Changes in the last limb, in turn, lead to anemia. Patients in our follow-up showed positive changes in most parameters when iron was added to its standard treatments when CHF was associated with anemia. This was due to the fact that the clinical condition of patients decreased from 6.67 ± 0.24 to 4.19 ± 0.16 points or improved by 56.7% ($p<0.01$), the level of resistance to physical load increased from 279.7 ± 11.2 to 406.1 ± 11.2 meters, increased by 68% ($p<0.05$), quality of life 50.0 ± 1.4 to 30.3 ± 1.0 also confirms a 60% ($p<0.01$) positive change.

Conclusion. 1. In case of chronic heart failure with anemia, after complex treatments with the addition of iron to its standard treatment, the level of iron in the blood in the main group increased 4.9 times ($p<0.001$), ie from 7.9 ± 0.2 mmol / l to 39.1 ± 1.1 mmol / l ($p <0.001$).

2. The renal fibrosis marker TGF-β_1 in the blood was reliably differentiated from 2591.0 ± 108.4 and 755.0 ± 18.87 pg / ml in chronic heart failure and anemia ($p<0.001$). This indicator confirms that fibrous processes in the kidneys are clearly manifested in anemia. After complex treatments with the addition of iron, TGF-$\beta_1$decreased by 2.25 times ($p<0.001$).

3. In chronic heart failure with anemia, the clinical condition of patients decreased from 6.67 ± 0.24 to 4.19 ± 0.16 points or improved by 56.7% ($p<0.01$), the level of resistance to physical exertion increased from 279.7 ± 11.2 to 406.1. ± 11.2 meters, an increase of 68% (p.050.05), and the quality of life changed from 50.0 ± 1.4 to 30.3 ± 1.0, a positive change of 60% ($p<0.01$).

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