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ASSESSMENT OF THE EFFICIENCY OF BIOREGULATOR DRUGS IN THE TREATMENT OF OSTEOARTHRITIS IN THE CLIMACTERIC PERIOD WITH ENDOTHELIAL DYSFUNCTION

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Abstract. In recent years, molecular bioregulatory drugs have come into practice for the treatment of OA. Bioregulatory drugs consist of several components (usually of natural origin) that affect many processes simultaneously as part of the anti-inflammatory response. Recently, the use of bioregulatory drugs Traumel S and Zeel T in the pathogenetic treatment of OA has justified in clinical practice. Traumel S is a bioregulatory agent of plant and mineral origin, containing 14 components, having anti-inflammatory, exudative, regenerating, analgesic and immunomodulatory effects.

The purpose of the study is to evaluate the effectiveness of bioregulatory drugs in the treatment of osteoarthritic patients in the climacteric period with endothelial dysfunction. From 2020 to 2022, 105 climacteric female patients with a confirmed diagnosis of OA of the knee joint, registered in the arthrological IADC department of the multidisciplinary clinic of the Tashkent Medical Academy (TMA), receiving inpatient treatment in the departments of cardiorheumatology and rheumatology, were involved in this research work. They analyzed the clinical course of the disease and the results of laboratory and instrumental examinations. For prospective analysis, the patients were divided into two groups: Group I consisted of female patients with premenopausal OA. Group II consisted of postmenopausal female patients with OA during menopause.

In the obtained results, the clinical and laboratory activity indicators of the disease reliably decreased in a statistically significant manner in the group of patients treated with bioregulatory drugs compared to traditional treatment. Also, indicators of endothelial dysfunction were improved. In UVD and MRI, degenerative changes in bones and joints showed positive dynamics.

In conclusion, in the treatment of OA patients in the climacteric period, the use of bioregulatory drugs (Traumel S and Zeel T) in addition to traditional treatment reduces the frequency of degenerative changes in the joints by reducing the clinical laboratory activity level of the disease, improving endothelial dysfunction, and improving the quality of life of patients.

Keywords: osteoarthritis, endothelial dysfunction, bioregulatory drugs, Zeel T, Traumel S

Based on the results of scientific research in recent years, the situation regarding OA has changed radically, and more and more scientists are coming to the conclusion that OA can be successfully treated in the early stages [1,17]. For example, modern researchers interpret all the components of the joint as an integral part of the body and say that not only the cartilage tissue, but also the subchondral

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bone, synovial shell, connective apparatus of the joint, muscles and elements of the nervous system responsible for innervation of the biological structures of the joint are involved in the pathological changes in OA [3] are promoting scientific views [2]. Thus, despite the fact that the important pathogenetic processes in OA mentioned above have been studied, several difficulties remain in the treatment of this disease in the practice of doctors[10,12,13]. The fact that bioregulatory drugs are one of the promising methods of treating rheumatological diseases, especially OA, in clinical practice has been confirmed in a number of scientific research works [4]. The main manifestations of these drugs are Zeel T and Traumel S, which are multicomponent preparations containing metabolic factors, herbal and biological ingredients. They provide chondroprotective and chondrostimulating, anti-inflammatory, analgesic, regeneration and immunostimulating effects [9,11,14,15]. They also have the property of stimulating the production of synovial fluid, which improves metabolic processes in the ankle[5]. It also helps to improve the elastic properties and hydrophilicity of intervertebral discs. It also has a trophic, metabolic, regenerating, analgesic, anti-inflammatory effect on tendons, ligaments and synovial tissue walls[6-8]. Bioregulatory drugs have a systemic approach to the pathophysiology of pain syndrome, affect the entire cascade of inflammation and restore the homeostasis of destructive tissues [16,18].

Purpose. to evaluate the effectiveness of Traumel S and Zeel T drugs in OA patients in the climacteric period.

Materials and methods. From 2020 to 2022, 105 climacteric female patients with a confirmed diagnosis of OA of the knee joint, registered in the arthrological IADC department of the multidisciplinary clinic of the Tashkent Medical Academy (TMA), receiving inpatient treatment in the departments of cardiorheumatology and rheumatology, were involved in this research work. A prospective analysis of patients was carried out in order to fulfill the tasks assigned to the research work. They analyzed the clinical course of the disease and the results of laboratory and instrumental examinations. For prospective analysis, the patients were divided into two groups: Group I consisted of 48.2±5.1-year-old female patients with premenopausal OA (n=51). Group II consisted of 50.1±5.3-year-old female patients (n=54) with OA during menopause.

The American College of Rheumatology and European Antirheumatic League (ACR)/EULAR) criteria were used to diagnose OA. Each patient involved in the study was filled out a separate individual card in order to record the examinations used. It combined the results of subjective and objective examination of the patient and included the following indicators:

- anamnestic data of patients, presence of comorbid pathology;
- joint syndrome intensity and indicators of its functional state (Visual analog scale (VAS), Leken indices) and their changes in dynamics;
- x-ray of knee joints (based on Kellgren-Lawrence criteria);
- magnetic resonance imaging (MRI);
- ultrasound examination (UVD) data;
- the results of the goniometry examination and their dynamic changes in order to assess the range of movements in the knee joint;

 results of laboratory analyzes (in dynamics GBA, CRP, RF, blood sugar index, ALT, AST, bilirubin, cholesterol);
 VEGF, MCP-1, NO
 Estradiol, FSG, LG
 medicines taken based on the patient's treatment recommendations.

Conventional radiographs of the joints of the hands and feet were performed in all patients. For the analysis of changes in the structure of the joint, a standard X-ray of the knee joint in a straight and lateral projection was carried out, using the Kellgren-Lawrence method. Ultrasound examination of the joints was used to determine the structural disorders formed in the joint, and was carried out using SonoScape S20. To determine the changes in the joint structure, magnetic resonance imaging (MRT - Siemens Magnetom C 0.35T model) was used. Analysis of the obtained results was carried out using the software package STATISTICA (StatSoft, version 6.1 – 8.0, USA) [18].

According to the data collected from the anamnesis of the patients involved in the research work, the average age of the patients at the time of the first symptoms of the disease in pre- and postmenopausal women with OA was 53.3±1.7. According to the average age of the patients and the duration of the disease, postmenopausal women predominated (57.1±4.2 and 5.1±1.2). It can also be seen that the average values of the body weight index in the representatives of this group increased depending on the average age of the patients and the duration of the disease (Table 1).

Table 1

General clinical characteristics of pre- and postmenopausal female patients divided by primary OA diagnosis (n=105)

Groups	Average age of patients	Disease duration (in years)	Average IMB of patients (kg/sm^2)
I Group (n =54)	49,5±2,6	3,2±1,2	32,13±2,0
II Group (n=51)	57,1±4,2	5,1±1,2	33,14±4,5

Analyzing the general clinical and laboratory parameters of pre- and postmenopausal women with primary OA, it was noted that the average duration of morning sickness did not exceed 10.5±5.4 minutes. VAS and Leken indices were 70.1±1.5 and 16.1±0.4, respectively. Symptoms of synovitis were detected in only 24% of patients. The number of painful and swollen joints was 2.8±1.5 and 2.1±0.8, respectively. When the functional insufficiency of the joints was studied, the presence of II functional class was observed in the majority of women with OA (54.8%). In 5% of them, we witnessed that the changes in the joints characteristic of the disease did not lead to functional deficiency. Of the indicators of inflammation, no strong negative dynamics were noted inC-reactive protein and erythrocyte sedimentation rate (23±0.1 and 20.2±1.5) (Table 2).

Table 2
General clinical and laboratory parameters of pre- and postmenopausal women with primary OA

Symptoms	Indicators (n=105)
Articular syndrome	
Duration of morning sickness, min.	10,5±5,4
Pain, VAS, mm	70,1±1,5
Number of painful joints	2,8±1,5
Number of swollen joints	2,1±0,8
The presence of synovitis, %	24
Leken index	16,1±0,4
Functional insufficiency of joints (%)	
0 class	5
I class	29,2
II class	54,8
III class	11
Laboratory indicators	
C-reactive protein, mg/l	23±0,1
Erythrocyte sedimentation rate, mm/s	20,2±1,5

Results. The chart below shows the mean age distribution of pre- and postmenopausal women with OA by group in percentages. According to him, the majority of patients in group I (64%) were women aged 41-50. The smallest percentage of them (7%) consisted of patients aged 51-60 years. On the contrary, women in the II group in this age range had an advantage with 48%. The next places were (37%) 41-50 and (5%) 61-70-year-old postmenopausal women (Figure 1).

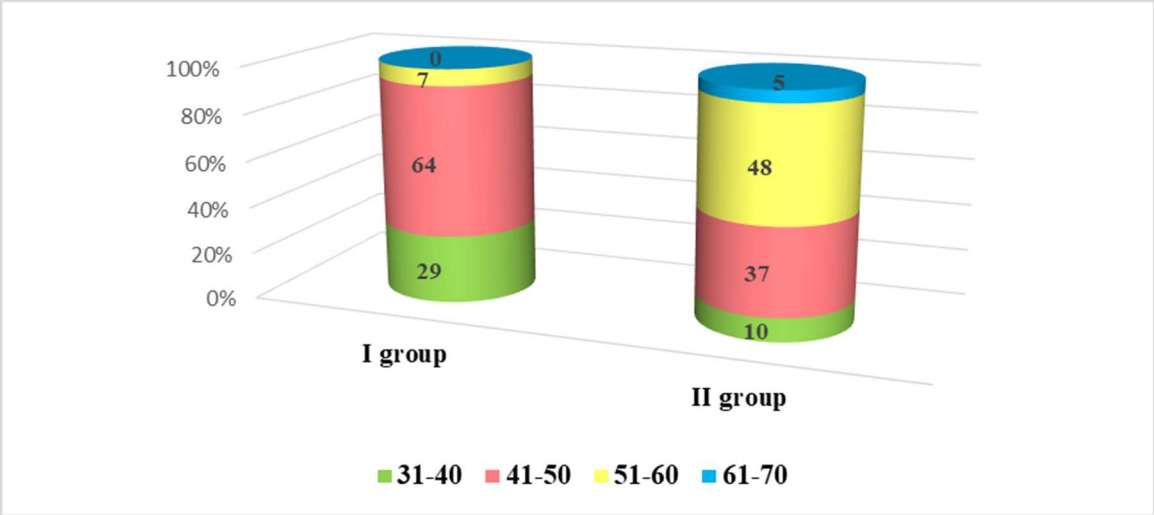


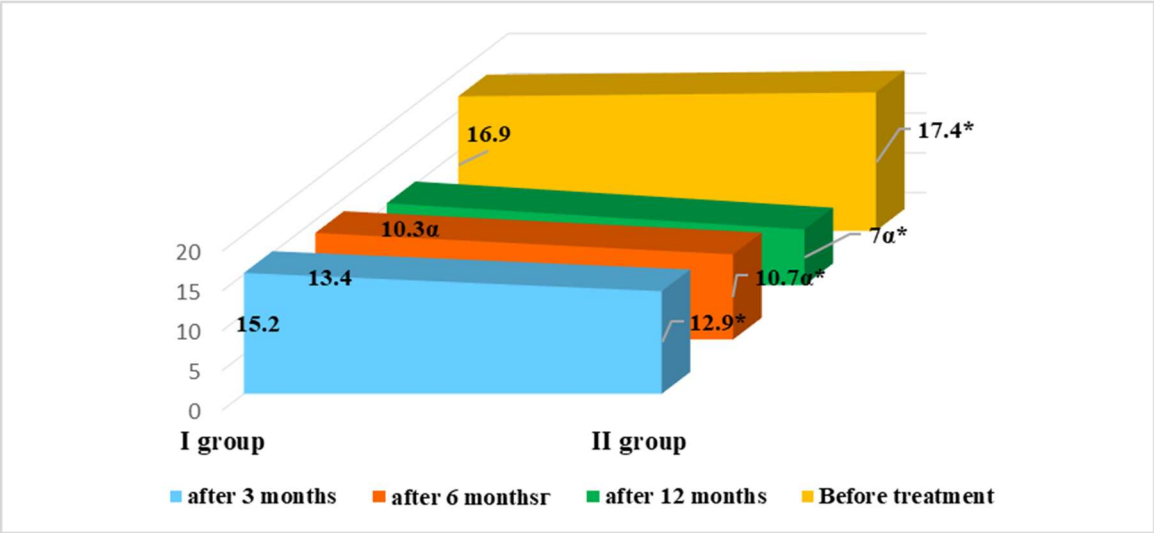
Figure 1. Distribution of mean age of pre- and postmenopausal women with OA (%)

According to the method of pharmacotherapy, patients were divided into two groups:

Group 1 patients with OA treated by conventional methods aged 49.5±2.6 (n=54) were recruited. acceptance of nonsteroidal anti-inflammatory drugs (100 mg of nimesulide 2 times a day for 14 days and depending on extioj in the following days); On the 6th month, taking a drug from the chondroprotector group (chondroitin sulfate 500 mg twice a day) per os.

Female patients with OA aged 57.1±4.2 years (n=51) were selected for the 2nd group. Bioregulatory drugs (Zeel T + Traumel S) were recommended along with the use of chondroprotectors. Zeel T was taken from 1 tablet 3 times a day for 8 weeks. Traumel S 2 ml was administered intramuscularly every day for 10 days. A combination of Zeel T and Traumel S drugs was injected around the affected joint by biopuncture every day for 5 days. Both gurus were advised to lead a healthy lifestyle, correct diet and physical fitness, and perform therapeutic physical exercises in addition to various treatment methods.

Clinical activity indicators of OA were reassessed after 3, 6, and 12 months in patients who received conventional and combined treatment regimens. According to him, a decrease in the WOMAC index was observed in both groups against the background of treatment. This index decreased statistically significantly by the 6th month of treatment in patients with OA who received combined treatment (17.4 vs. 10.7; r<0.05). In the group of patients who received traditional treatment, the statistically significant decrease of this indicator occurred only after 12 months (16.9 and 10.3; r<0.05). In group II patients, by this time, this indicator decreased by 2.5 times (17.4 and 7; r<0.05). Also, the values of the WOMAC index in the group recommended combined pharmacotherapy were statistically significantly lower than the indicators of patients who received conventional treatment (r<0.5) (Fig. 2).

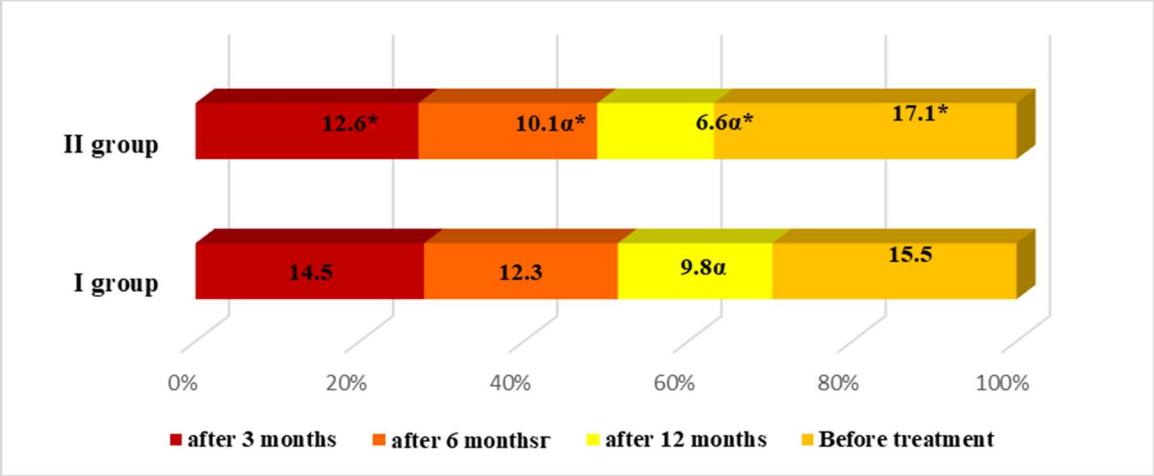


Note: *- r<0.5-1 is a reliable difference compared to group indicators

α- r<0.05-reliable difference from pre-treatment values

Figure 2. Dynamics of change of WOMAC index by groups (score) against the background of treatment

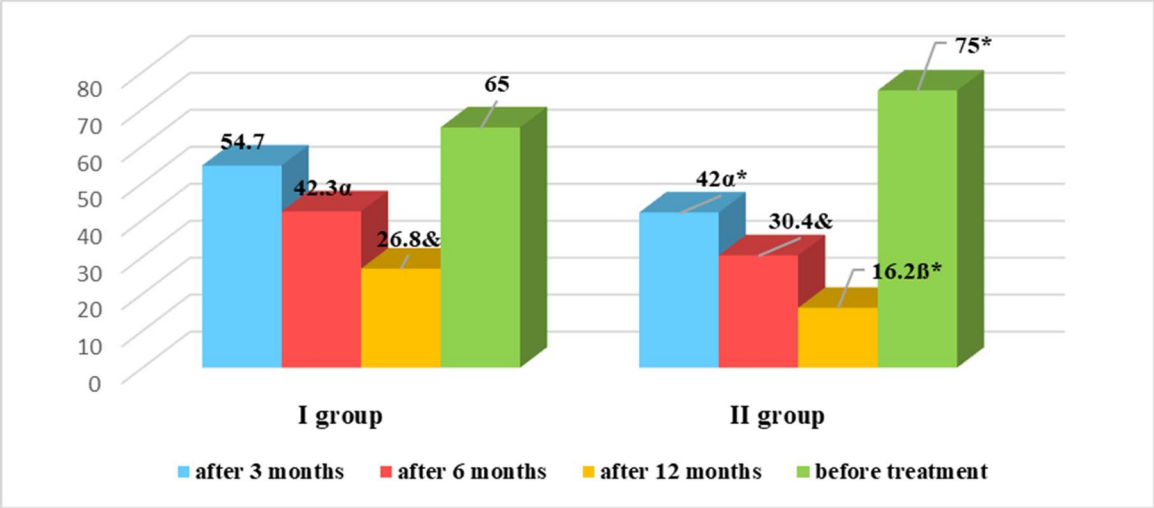
Figure 3 below shows the dynamics of changes in the Lequene index by groups against the background of pharmacotherapy. In it, we witnessed a statistically significant decrease of this index in patients of group II, who received combined drugs, compared to indicators of group I, who received traditional treatment ($r<0.5$). In group II patients, a convincing decrease of this indicator began from the 6th month of treatment (17.1 and 10.1; $r<0.05$), while in patients who received conventional treatment, positive dynamics compared to pre-treatment values were observed only after 1 year (15.5 and 9.8; $r<0.05$) (Figure 3).



Note: *- r<0.5-1 is a reliable difference compared to group indicators
α- r<0.05-reliable difference from pre-treatment values

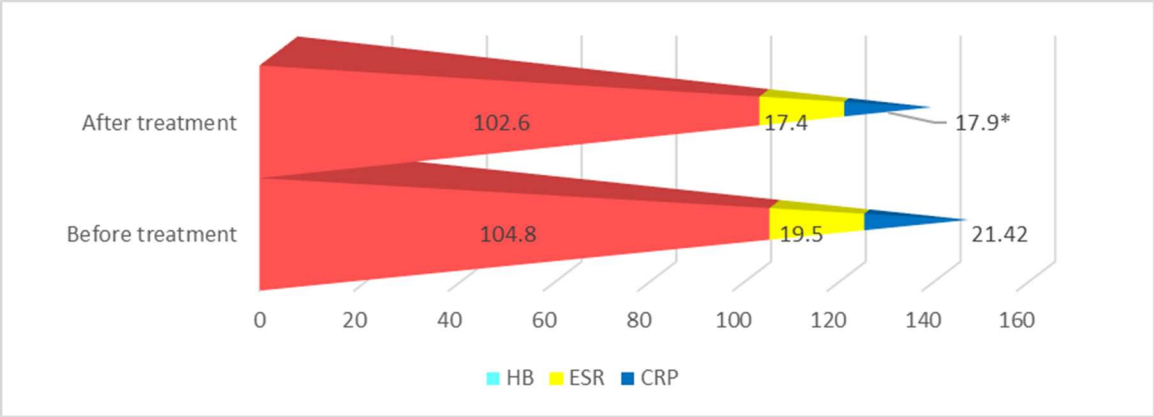
Figure 3. Dynamics of change of the Lequene index by groups (score) against the background of treatment

In patients with OA who were prescribed traditional and combined pharmacotherapy, the VASh index recorded a positive dynamic faster than the WOMAC and Lequene indices. That is, in the women treated with the combined method, within the first 3 months, the VASh index was reliably reduced from 75 to 42 ($r<0.01$). In the group recommended traditional treatment, such a change occurred only after half a year (65 and 42.3; $r<0.01$). Against the background of one-year pharmacotherapy, the VASh index decreased up to 3 times in group I (65 and 26.8; $r<0.001$), and almost 4 times in group II (75 and 16.2; $r<0.0001$). In patients with OA who were prescribed combined pharmacotherapy, we saw that the VAS index decreased to statistically significant numbers ($r<0.5$) (Fig. 4).

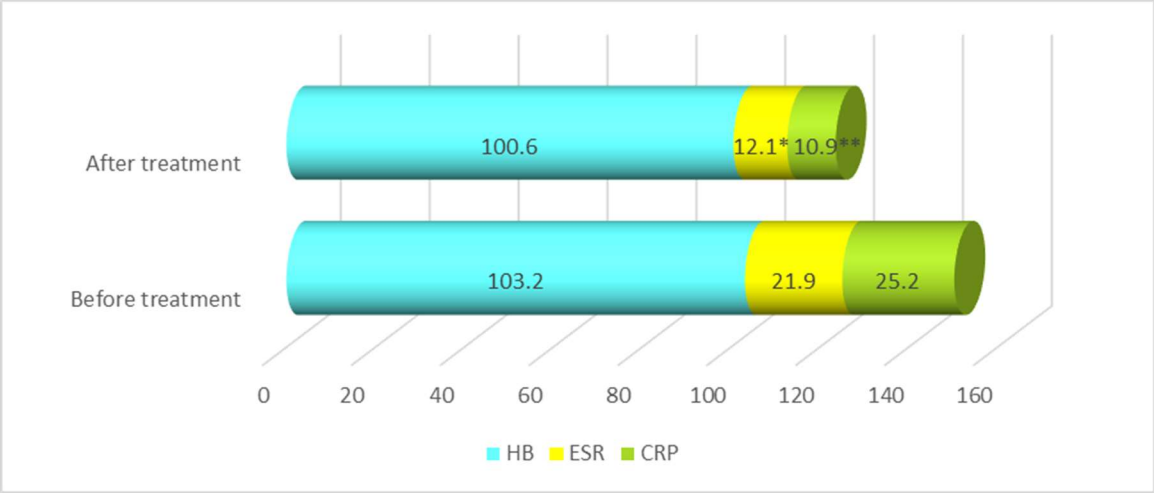


Note: *- r<0.5-1 is a reliable difference compared to group indicators
α- r<0.01; & - r<0.001; ß- r<0.0001-reliable difference compared to pre-treatment indicators
Figure 4. Dynamics of VAS index changes by groups (points) against the background of treatment

In the analysis of the changes in the average indicators of ESR, CRP and hemoglobin in the blood against the background of treatment of women with OA in group I, statistically significant positive shift was almost not noted. Only the level of CRP significantly decreased compared to pre-treatment values (21.42 and 17.9 respectively; r<0.5) (Figure 5).



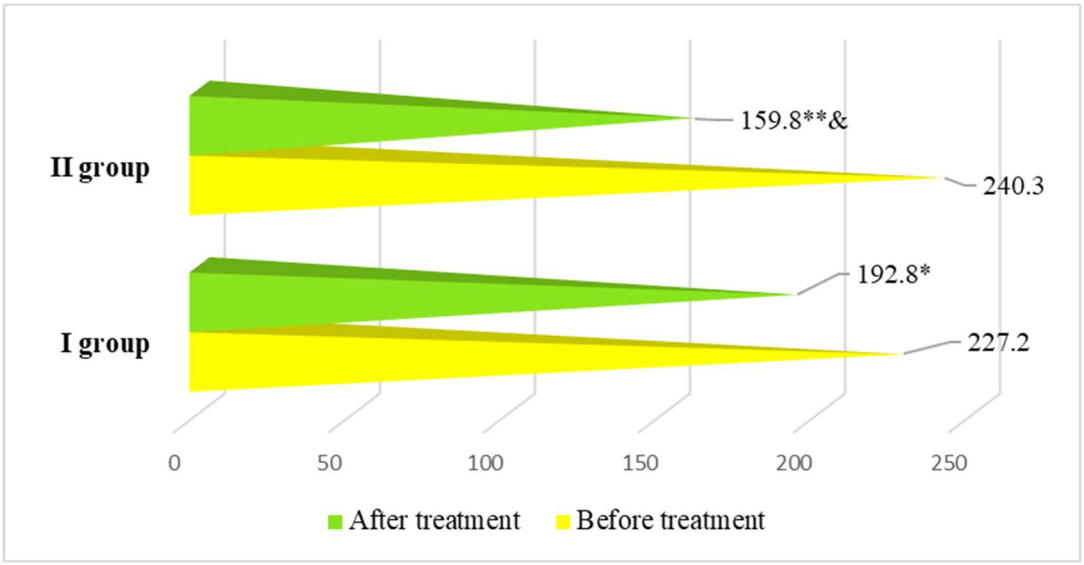
Note: *- r<0.5-Reliable difference compared to pre-treatment values
Figure 5. Analysis of changes in the average values of ESR, CRP and hemoglobin in blood (mm/s; mg/l; g/l) against the background of treatment in women with OA of group I
In contrast to traditional treatment, we witnessed a statistically significant decrease in not only CRP but also ESR levels in group II patients who received combined pharmacotherapy. Admittedly, the level of CRP in group II patients was significantly reduced in diagnostically significant titers compared to conventionally treated group patients (25.2 vs. 10.9; r<0.0005). There were no statistically significant changes in ESR in group I patients, but in the group of OA patients treated with combined treatment, its amount decreased reliably from 21.9 mm/s to 12.1 mm/s (r<0.005) (Fig. 6).



Note: *- r<0.005; **- r<0.0005-Reliable difference compared to pre-treatment values

Figure 6. Analysis of changes in the average values of ESR, CRP and hemoglobin in blood (mm/s; mg/l; g/l) against the background of treatment in women with OA of group II

The effectiveness of the recommended pharmacotherapy was evaluated according to the clinical and laboratory activity of the disease and the levels of endothelial dysfunction. The change of MCP-1 levels against the background of pharmacotherapy is shown in Figure 7 below. According to this, the amount of MCP-1 decreased statistically significantly in both groups as a result of treatment, but the rate of decrease in group II was reliably higher than the values before treatment and group I (240.3 and 159.8, respectively; r<0.0005) and (159.8 and 192.8 respectively; r<0.0001). In group I, only positive dynamics were observed compared to pre-treatment indicators (227.2 and 192.8, respectively; r<0.005).

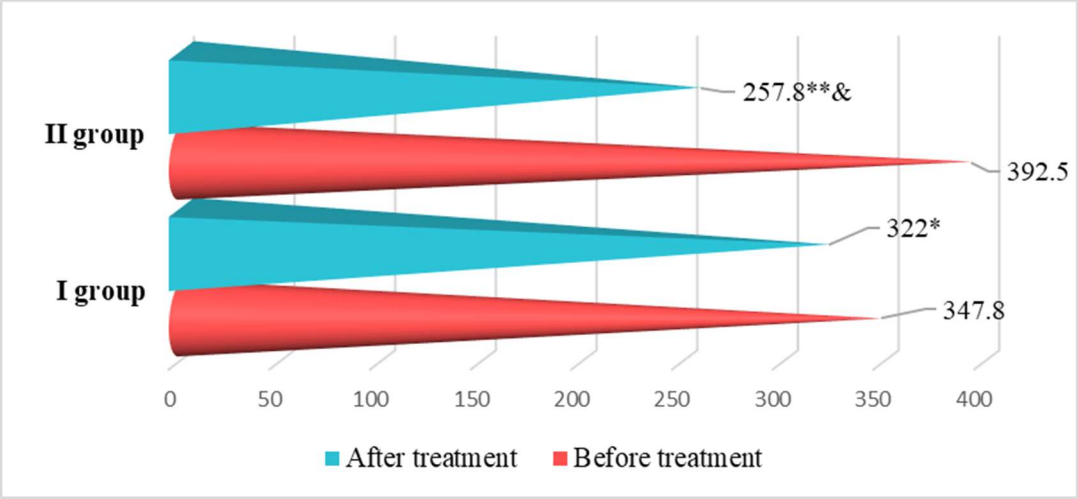


Note: *- r<0.005; **- r<0.0005 reliable difference compared to pre-treatment values

&- r<0.0001-1- reliable difference compared to group indicators

Figure 7. Group-by-group comparison of changes in mean MCP-1 levels (ME/ml) over treatment background

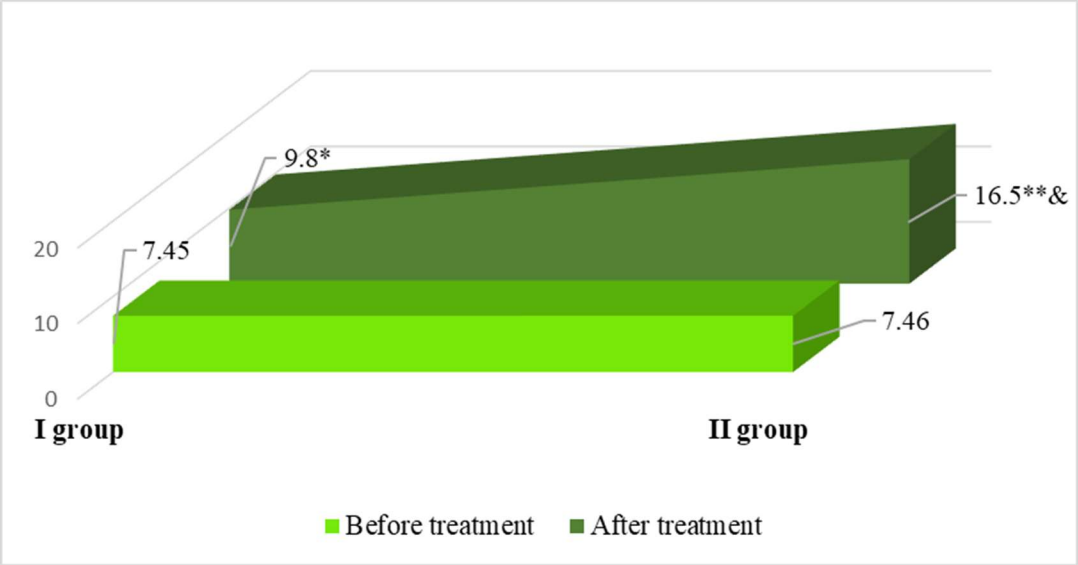
Also, the effectiveness of conventional and combined treatment methods was examined in the example of changes in the level of VEGF. According to him, as a result of treatment, VEO'O decreased statistically reliably in both groups, but the indicators of group II, which received combined treatment, not only decreased more reliably than before treatment, but also compared to the indicators of group I (392.5 and 257.8, respectively; r<0.0005) and (257.8 and 322 respectively; r<0.0001). In group I, only a statistically significant decrease was noted compared to pre-treatment values (347.8 and 322, respectively; r<0.005) (Figure 8).



Note: *- r<0.005; **- r<0.0005 reliable difference compared to pre-treatment values
&- r<0.0001-1- reliable difference compared to group indicators

Figure 8. Comparative analysis of changes in the average amount of VEGF in the treatment background by groups (ME/ml)

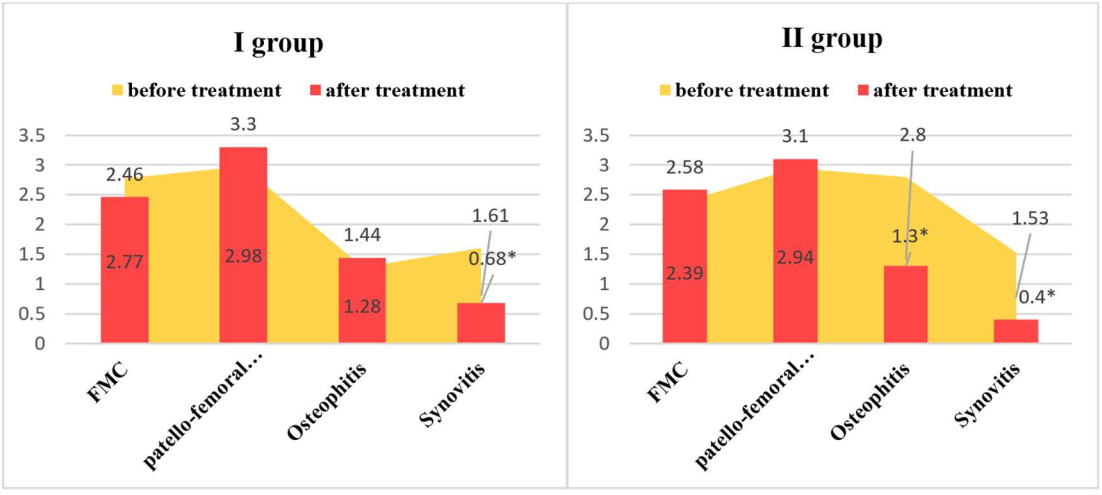
It is known that NO has a strong antioxidant property, and the reduction of its titers is an important factor in the development of endothelial dysfunction. In our research work, in addition to MCP-1 and VEGF which determine endothelial dysfunction, changes in the amount of NO were also taken into account. In this case, both methods of pharmacotherapy led to a reliable increase in NO titer in patients with OA (7.45 and 9.8, respectively) (r<0.5) and (7.46 and 16.5, respectively) (r<0.0005). Even the post-pharmacotherapy scores of group II were statistically significantly higher than the post-treatment scores of the conventionally treated group (16.5 vs. 9.8, respectively)(r<0.0005). In the conventional treatment group, there was only a statistically significant shift compared to pre-treatment values (7.45 and 9.8, respectively; r<0.5) (Figure 9).



Note: *- r<0.5; **- r<0.0005 reliable difference compared to pre-treatment values
&- r<0.0005-1- a reliable difference compared to the indicators in the group

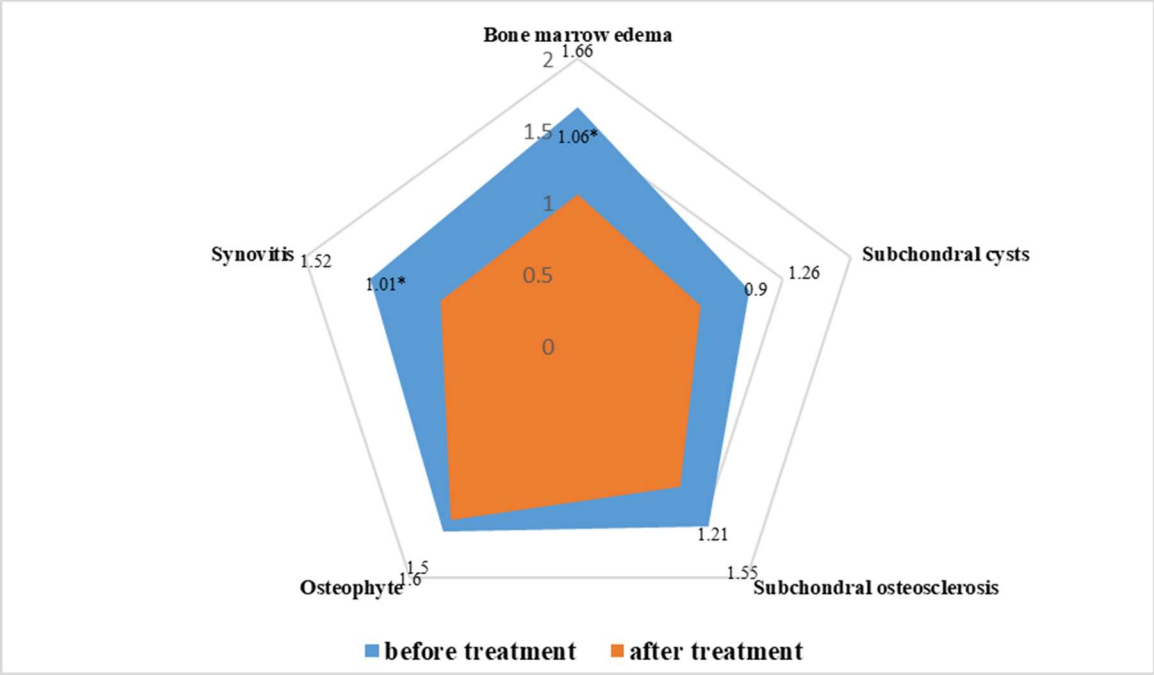
Figure 9. Group-wise comparison of changes in mean levels of NO over treatment background (ME/ml)

In diagram 10 below, the changes in the destruction, osteophyte and synovitis values of the femoral medial condyle (FMC), patello-femoral joint (PFJ) tendons determined by ultrasound examination against the background of 12 months of combined and conventional pharmacotherapy were analyzed by groups. According to it, we observed a statistically insignificant decrease in the destruction of the femoral medial condyle, patellofemoral joint (PFJ), and osteophyte indicators in patients of group I, who were treated conventionally, compared to the values before treatment. However, synovitis levels were statistically significantly reduced compared to pre-treatment values (1.61; 0.68; r<0.05). In the group of patients who received the combined treatment method, not only synovitis, but also osteophyte levels were reliably reduced compared to the values before treatment (1.53; 0.4; r<0.05 and 2.8; 1.3; r<0, 05).



Note: *- r<0.05-reliable difference from pre-treatment values
Figure 10. Dynamics of changes in the parameters determined by ultrasound examination against the background of pharmacotherapy (score) by groups

Diagram 11, illustrated below, shows the dynamics of changes in OA-specific MRI parameters after 12 months of pharmacotherapy. According to it, we witnessed a statistically insignificant reduction of subchondral osteosclerosis, cyst and osteophyte indicators compared to pre-treatment values. However, bone marrow edema and synovitis levels were statistically significantly reduced compared to pre-treatment values (1.66; 1.06; r<0.5 and 1.52; 1.01; r<0.5).



Note *- r<0.5 -reliable difference compared to pre-treatment indicators
Figure 11. The dynamics of changes in OA-specific MRI indicators in patients against the background of treatment

Conclusion. In the treatment of OA patients in the climacteric period, the use of bioregulatory drugs (Traumel S and Zeel T) in addition to traditional treatment reduces the frequency of degenerative changes of the joints by reducing the clinical laboratory activity of the disease, improving the conditions of endothelial dysfunction, and improves the quality of life of patients.

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