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EVALUATION OF THE EFFICIENCY OF BISPHOSPHONATES IN THE TREATMENT OF OSTEOPOROSIS IN THE CLIMACTERIC PERIOD

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Abstract

Osteoporosis (OP) is a widespread metabolic disease of the skeleton, leading to decreased bone strength and increased risk of fractures. OP is a disease of varying nature that affects all age groups, but is most common in older people. For a long time, doctors did not have serious tools to treat this insidious disease and mainly dealt with its consequences - fractures. We have witnessed the birth of a new group of drugs—bisphosphonates (BPs), which have significantly expanded the capabilities of clinicians in the treatment of OP and a number of other bone diseases, as well as calcium metabolism disorders. Modern medicine is based on a solid evidence base. All drugs recommended for use in clinical practice are subject to long-term, multi-stage clinical studies of effectiveness and safety. Possessing different biological activities, these drugs demonstrated one common property in clinical trials, which allowed them to be recommended for the treatment of OP: reducing the risk of fractures. The purpose of the study is to evaluate the effectiveness of bisphosphonates in the treatment of patients with OP in the climacteric period. From 2020 to 2022, 105 climacteric female patients with a confirmed diagnosis of OP 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 OP. Group II consisted of postmenopausal female patients with OP 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 bisphosphonates 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 OP patients in the climacteric period, the use of bisphosphonates (Zoledronic acid) 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: Osteporosis, Endothelial Dysfunction, Bisphosphonates, Zoledronic Acid.

The Seybold Report
ISSN 1533-9211

INTRODUCTION

Osteoporosis is a condition in which gradually decreasing bone mass and deteriorating bone structure leads to increased bone fragility and increased risk for fractures, particularly of the wrist, hip and spine (WHO 1994). This process progresses without symptoms until fractures occur or kyphosis becomes apparent. Thus osteoporosis is often described as a silent menace [16, 18].

Once fractures and deformities have occurred, pain may become a prominent problem and a challenge for people with osteoporosis and everyone involved with their care. Such established osteoporosis is a major cause of morbidity, mortality and reduced quality of life (Lips et al 2005) [1, 17].

Currently, four BPs are registered in our country and recommended for the treatment of OP: alendronate, risendronate, ibandronate and zoledronate. Modern medicine is based on a solid evidence base [6-8]. All drugs recommended for use in clinical practice are subject to long-term, multi-stage clinical studies of effectiveness and safety [10, 12, 13].

Possessing different biological activities, these drugs demonstrated one common property in clinical trials, which allowed them to be recommended for the treatment of OP: reducing the risk of fractures [2, 5].

However, working in the era of evidence-based medicine and reading reports on the results of multicenter, double-blind, placebo-controlled, randomized trials, doctors continue to test in practice the effectiveness of the proposed treatment methods, as doctors did in the days of our grandparents, assessing not only the advantages of the drugs [9, 11, 14, 15], but also their disadvantages, side effects and raising questions that have yet to be answered. In our center, for more than 10 years, all BPs registered in Russia and recommended for the treatment and prevention of OP have been used in clinical practice.

Already the first results of treatment of OP BP made it possible to note a significant increase in bone mineral density (BMD) after 6 months of treatment with alendronate. We then received ibandronate, which was administered orally once a month, which greatly simplified the treatment of postmenopausal OP [3, 4].

Purpose. To Evaluate the effectiveness of Zoledronic acid in OP patients in the climacteric period.

MATERIALS AND METHODS

From 2020 to 2022, 105 climacteric female patients with a confirmed diagnosis of OP 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.

The Seybold Report
ISSN 1533-9211

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 OP (n=51). Group II consisted of 50.1±5.3-year-old female patients (n=54) with OP during menopause.

The American College of Rheumatology and European Antirheumatic League (ACR)/EULAR) criteria were used to diagnose OP. 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 OP 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).

The Seybold Report
ISSN 1533-9211

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 OP 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 OP, 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 OP (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 OP

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

The Seybold Report
ISSN 1533-9211

RESULTS

The chart below shows the mean age distribution of pre- and postmenopausal women with OP 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).

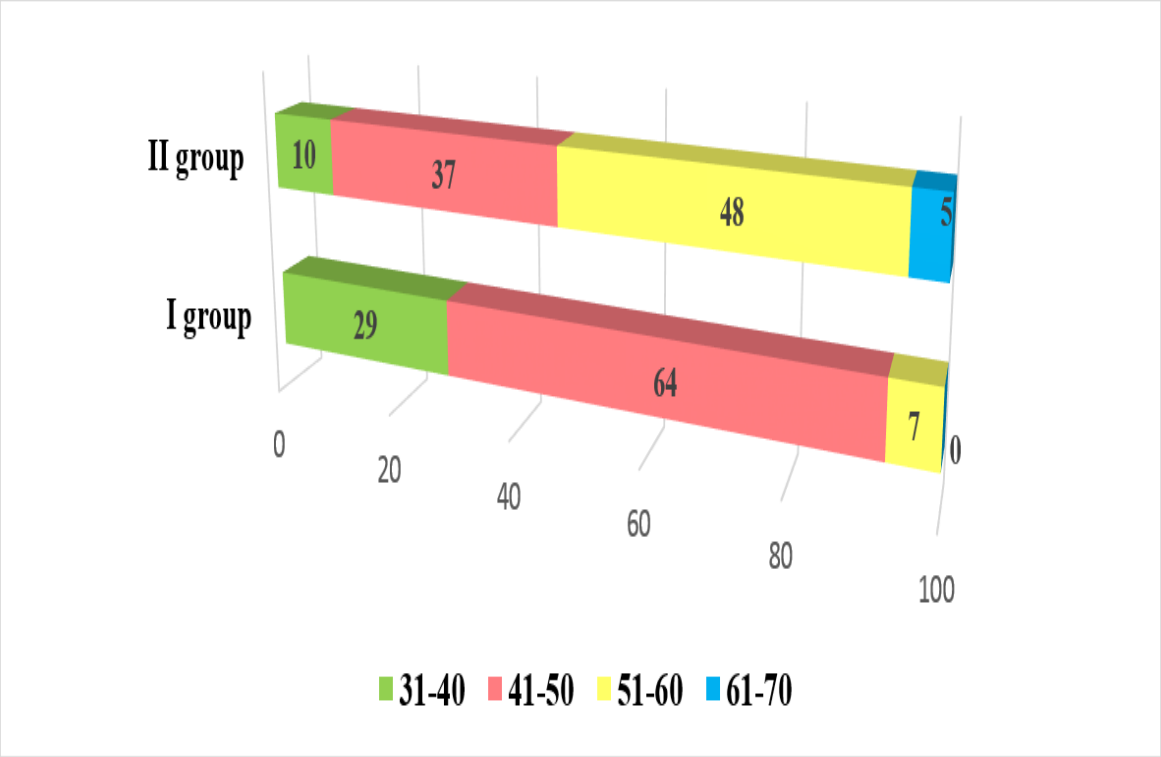


Figure 1: Distribution of Mean Age of Pre- and Postmenopausal Women with OP (%)

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

Group 1 patients with OP 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, calcium 1000ME/day and vitamin D (5000ME/day).

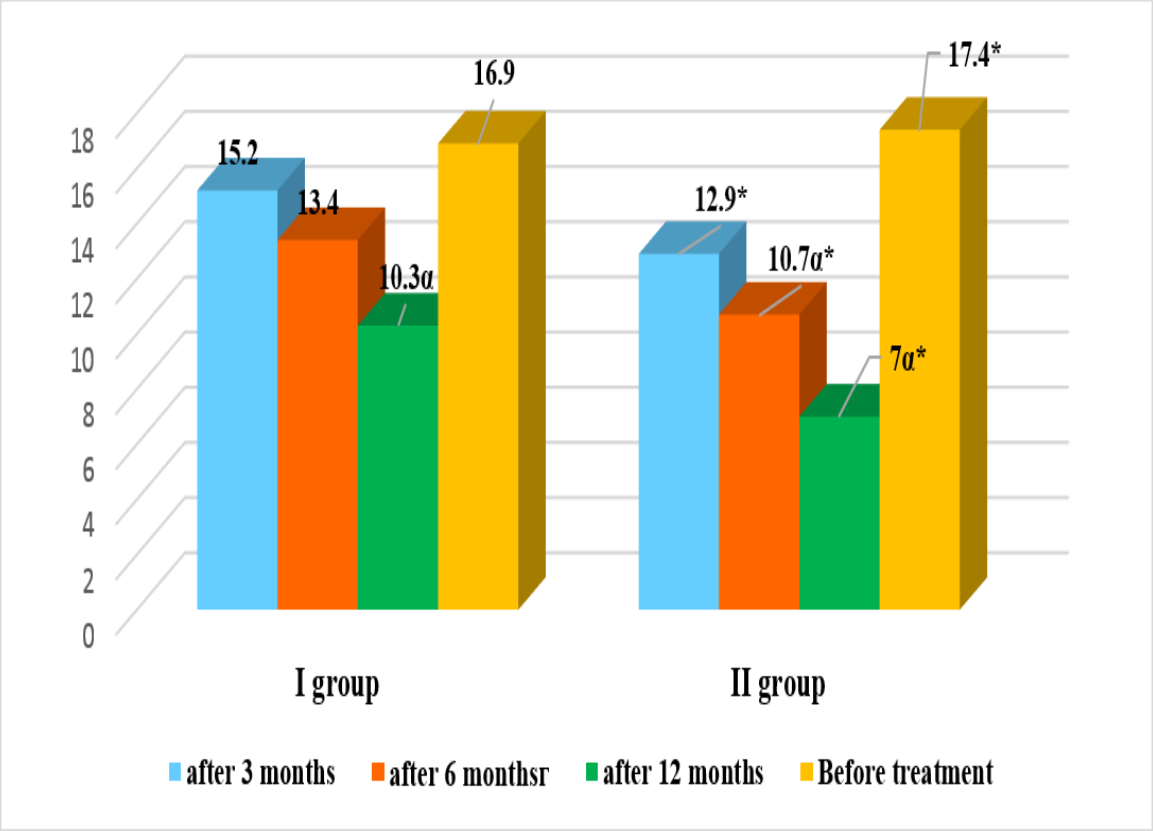
Female patients with OP aged 57.1±4.2 years (n=51) were selected for the 2nd group. Bisphosphonates (Zoledronic acid) were recommended along with the use of calcium 1000ME/day. Zoledronic acid 5mg (100ml) was taken intravenous a day for year. Both gurus were advised to lead a healthy lifestyle, correct diet and physical fitness, and perform therOPeutic physical exercises in addition to various treatment methods.

The Seybold Report
ISSN 1533-9211

Clinical activity indicators of OP 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 OP who received combined treatment (17.4 vs. 10.7; $p<0.05$).

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; $p<0.05$). In group II patients, by this time, this indicator decreased by 2.5 times (17.4 and 7; $p<0.05$).

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 ($p<0.5$) (Fig. 2).



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

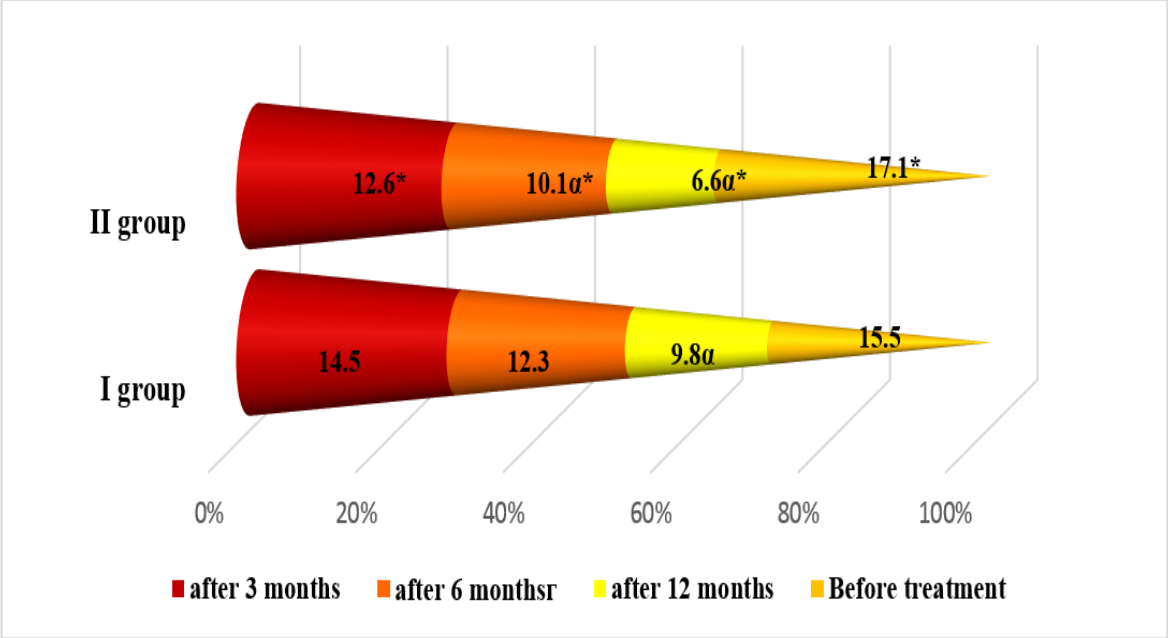
α-$p<0.05$-reliable difference from pre-treatment values

Figure 2: Dynamics of Change of WOMAC Index by Groups (score) Against the Background of Treatment

The Seybold Report
ISSN 1533-9211

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 ($p<0.5$).

In group II patients, a convincing decrease of this indicator began from the 6th month of treatment (17.1 and 10.1; $p<0.05$), 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; $p<0.05$) (Figure 3).



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

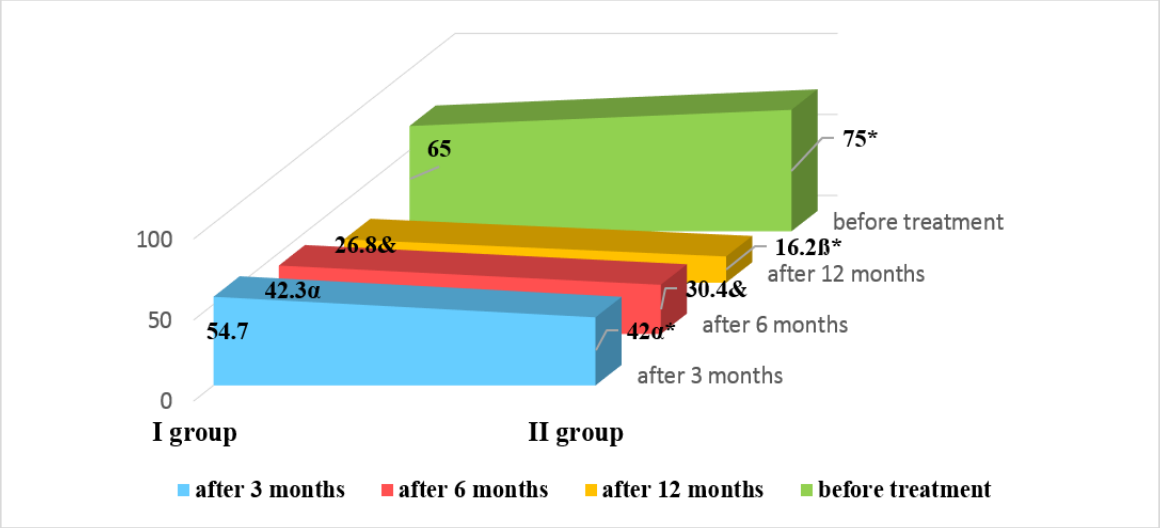
α- $p<0.05$-reliable difference from pre-treatment values

Figure 3: Dynamics of Change of the Lequene Index by Groups (score) Against the Background of Treatment

In patients with OP 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 ($p<0.01$). In the group recommended traditional treatment, such a change occurred only after half a year (65 and 42.3;$p<0.01$).

Against the background of one-year pharmacotherapy, the VASh index decreased up to 3 times in group I (65 and 26.8; $p<0.001$), and almost 4 times in group II (75 and 16.2; $p<0.0001$). In patients with OP who were prescribed combined pharmacotherOPy, we saw that the VAS index decreased to statistically significant numbers ($p<0.5$) (Fig. 4).

The Seybold Report
ISSN 1533-9211

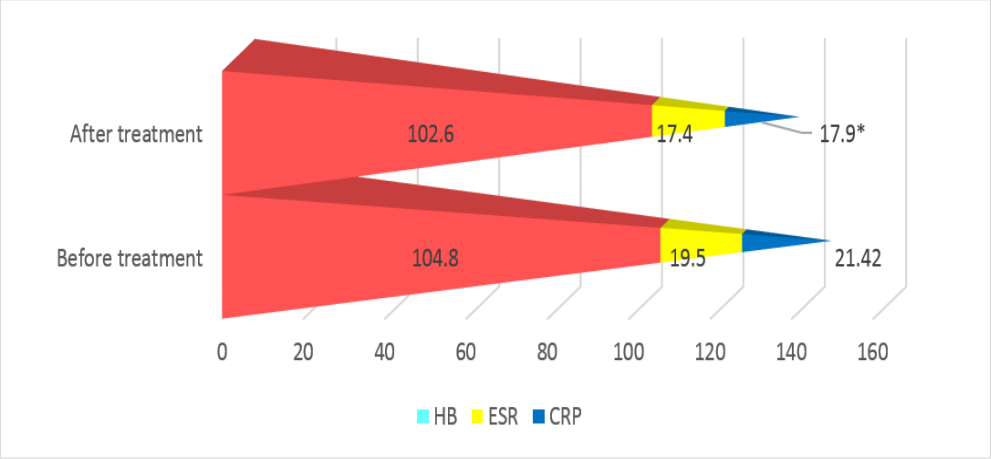


Note: *- p<0.5-1 is a reliable difference compared to group indicators

α- p<0.01; & - p<0.001; ß- p<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 OP 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; p<0.5) (Figure 5).

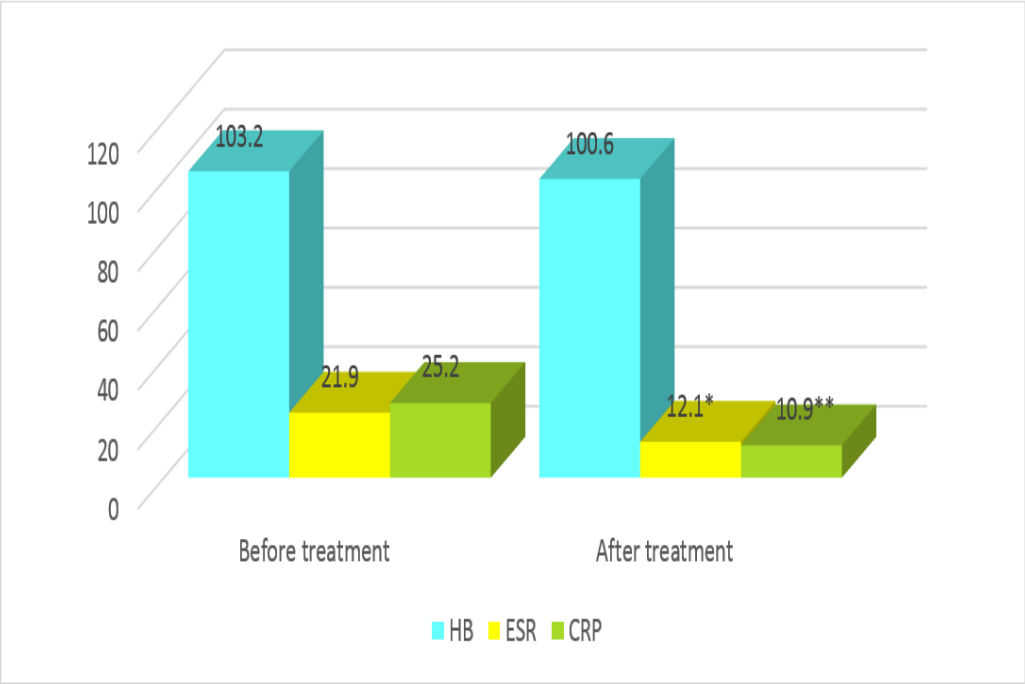


Note: *- p<0.5-Reliable difference compared to pre-treatment values

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 OP of Group I

ISSN 1533-9211

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 pharmacotherOPy. 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; $p<0.0005$). There were no statistically significant changes in ESR in group I patients, but in the group of OP patients treated with combined treatment, its amount decreased reliably from 21.9 mm/s to 12.1 mm/s ($p<0.005$) (Fig. 6).

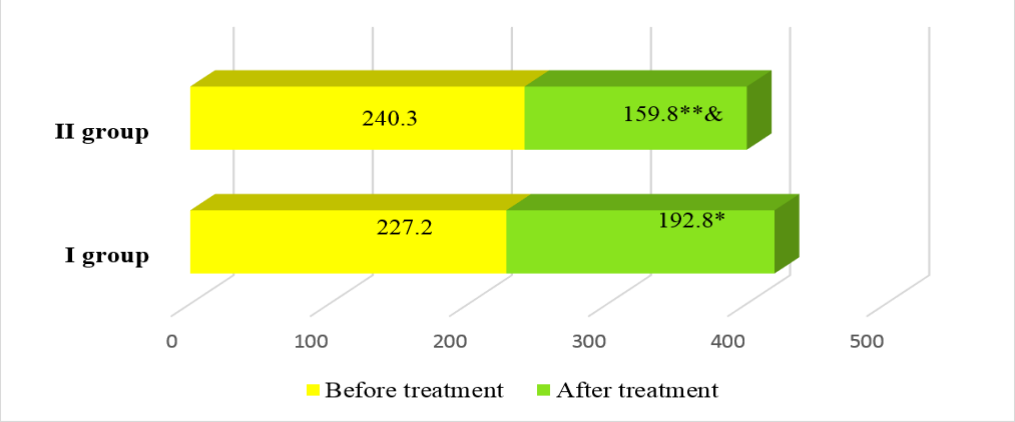


Note: *- $p<0.005$; **- $p<0.0005$-Reliable difference compared to pre-treatment values

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 OP of group II

The effectiveness of the recommended pharmacotherOPy 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 pharmacotherOPy 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; $p<0.0005$) and (159.8 and 192.8 respectively; $p<0.0001$). In group I, only positive dynamics were observed compared to pre-treatment indicators (227.2 and 192.8, respectively; $p<0.005$).

The Seybold Report
ISSN 1533-9211

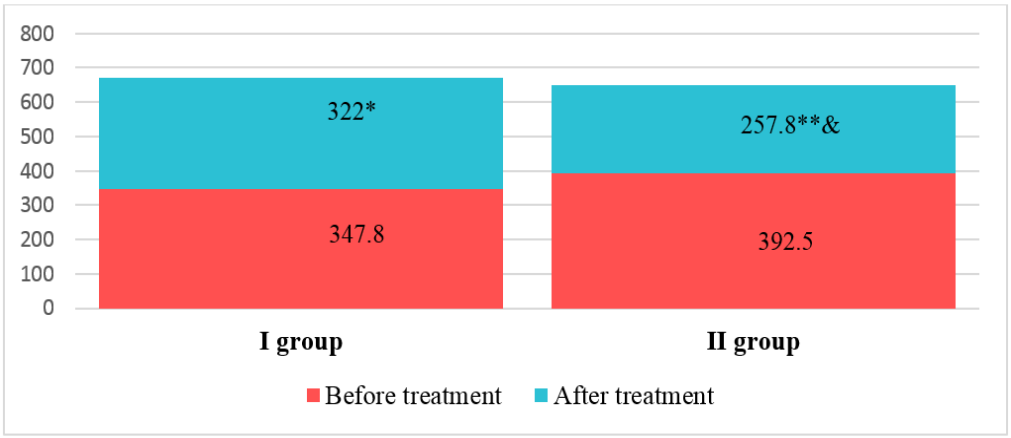


Note: *- p<0.005; **- p<0.0005 reliable difference compared to pre-treatment values

&- p<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, VEGF 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; p<0.0005) and (257.8 and 322 respectively; p<0.0001). In group I, only a statistically significant decrease was noted compared to pre-treatment values (347.8 and 322, respectively; p<0.005) (Figure 8).



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

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

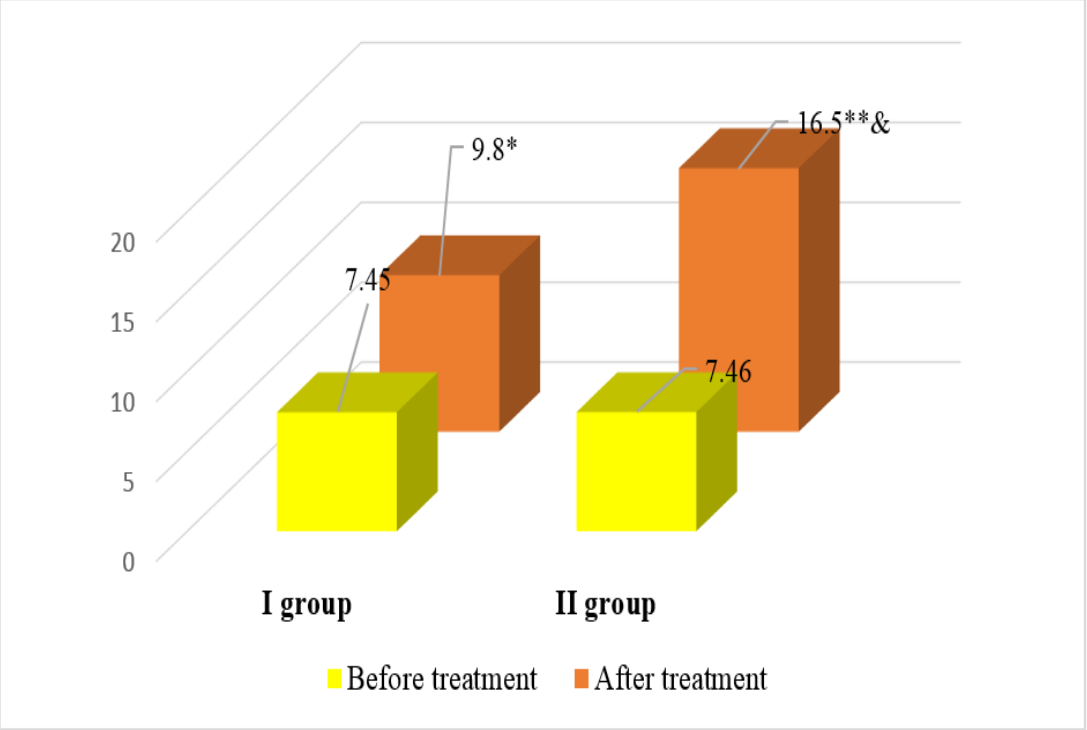
Figure 8: Comparative Analysis of Changes in the Average Amount of VEGF in the Treatment Background by Groups (ME/ml)

The Seybold Report
ISSN 1533-9211

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 pharmacotherOPy led to a reliable increase in NO titer in patients with OP (7.45 and 9.8, respectively) ($p<0.5$) and (7.46 and 16.5, respectively) ($p<0.0005$). Even the post-pharmacotherOPy scores of group II were statistically significantly higher than the post-treatment scores of the conventionally treated group (16.5 vs. 9.8, respectively)($p<0.0005$).

In the conventional treatment group, there was only a statistically significant shift compared to pre-treatment values (7.45 and 9.8, respectively; $p<0.5$) (Figure 9).



Note: *- $p<0.5$; **- $p<0.0005$ reliable difference compared to pre-treatment values

&- $p<0.0005$-1- a reliable difference compared to the indicators in the group

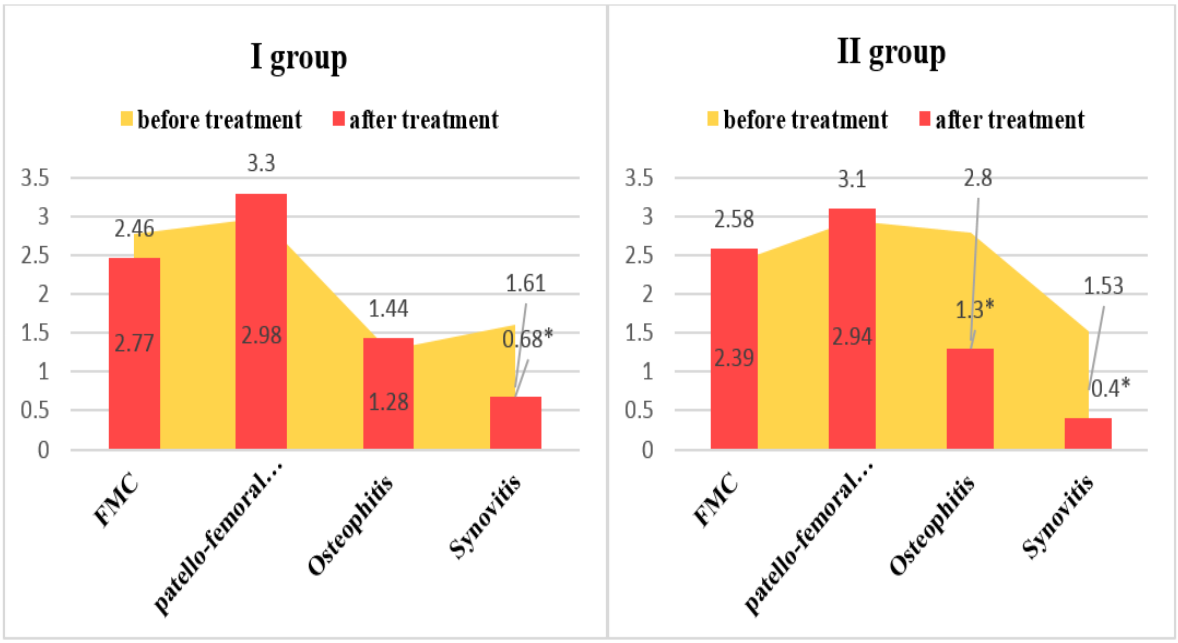
Figure 9: Group-Wise Comparison of Changes in Mean Levels of NO Over Treatment Background (ME/ml)

The Seybold Report
ISSN 1533-9211

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; $p<0.05$). 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; $p<0.05$ and 2.8; 1.3; $p<0, 05$).



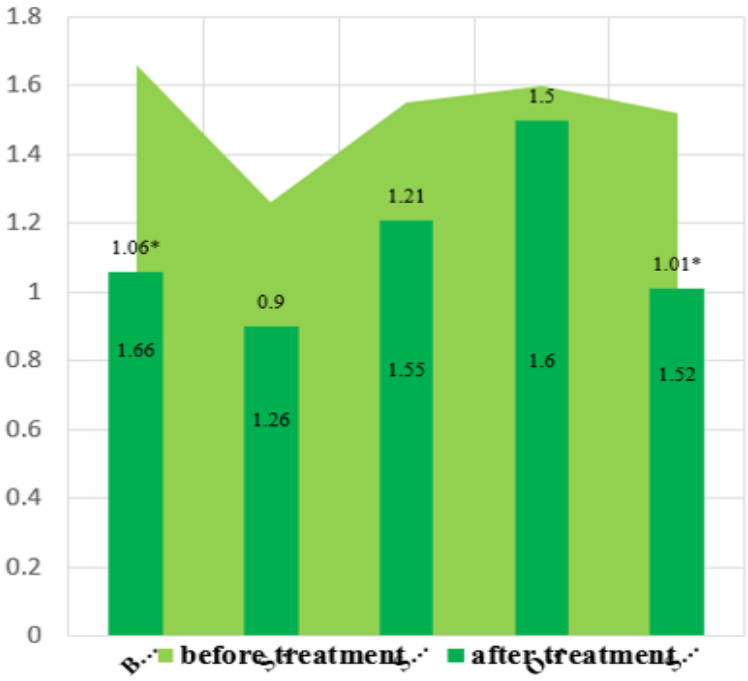
Note: *- $p<0.05$-reliable difference from pre-treatment values

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 OP-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; $p<0.5$ and 1.52; 1.01; $p<0.5$).

The Seybold Report
ISSN 1533-9211



Note *- p<0.5 -reliable difference compared to pre-treatment indicators

Figure 11: The Dynamics of Changes in OP-specific MRI Indicators in Patients Against the Background of Treatment

CONCLUSION

In the treatment of OP patients in the climacteric period, the use of bisphosphonates (Zoledronic acid) and calcium 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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The Seybold Report
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