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THE EFFECT OF COMBINATION THERAPY ON BONE METABOLISM

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Abstract: Combination therapy in both groups was significantly effective in influencing bone mineral density (BMD) L1-L4. Therapy using Forcal plus showed a significantly greater increase in BMD in the vertebrae. There was a significantly greater decrease in pain syndrome. In conclusion, it should be noted that Forcal plus is an effective treatment for osteoporosis (OP). Its long-term use in the complex therapy of various forms of OP leads not only to a progressive increase in BMD in the lumbar spine and proximal femur, but also to a decrease in the risk of vertebral fractures.

Keyword: osteoporosis, densitometry, BMD, calcium.

Introduction. Osteoporosis is a metabolic disease of the skeleton characterized by a decrease in bone mass and a violation of its quality (microarchitectonics), leading to bone fragility, which manifests itself as fractures with minor injury (when falling from a height no higher than one's own height or spontaneously). The most important goal of early diagnosis and treatment of osteoporosis is to prevent the first osteoporotic fracture and prevent an osteoporotic cascade of fractures [11]. Osteoporosis can be treated, but since there are no subjective warning signs of the disease before the fracture occurs, many patients are not diagnosed with osteoporosis in time and effective therapy is not prescribed at an early stage of the disease [8]. In all postmenopausal women and men aged 60 years and older, it is necessary to assess the risk of osteoporosis and fractures to determine the need for densitometry and to visualize the spine [27].

There are two risk factors for osteoporosis and fractures. Unmodified factors include old age, a history of adulthood fracture, Caucasian race, female gender, and dementia. Modifiable factors include smoking, estrogen deficiency, insufficient intake of calcium/vitamin D throughout life, alcoholism, visual impairment, frequent falls, inadequate physical activity [5].

Many diseases associated with osteoporosis: chronic kidney disease (CKD), COPD, bronchial asthma (hormone dependent), rheumatoid arthritis, hypo- and hyperthyroidism, hyperparathyroidism, diabetes mellitus, gastric resection and malabsorption syndrome, pancreatitis and enzyme deficiency, liver cirrhosis and liver failure, blood diseases, epilepsy (taking anticonvulsants drugs). In patients with CKD, all links in the regulation of phosphorus-calcium metabolism are disrupted, including a decrease in calcitriol production. The main reason for the decrease in the formation of 1.25(OH)2D3 is the destruction of its formation sites in the area of the renal proximal tubules. At the same time, under the influence of hyperphosphatemia, the activity of 1α-hydroxylase, which converts 25OND into 1,25 (OH)2 D3, decreases [1].

The results of numerous studies indicate that osteoporosis and atherosclerosis are associated not only with age of occurrence, but also have common pathogenetic mechanisms [6].

Data have been obtained indicating that osteoporosis, calcification of the aorta and heart valves and atherosclerotic vascular lesion are interrelated pathological processes. Vascular and bone tissue have a number of common morphological properties, and vascular calcification consists of the same components as bone tissue. According to an epidemiological study, each decrease in the BMD of the proximal radius by one standard deviation from the norm increased the risk of premature death over the next 2 years by 40 and especially death from stroke. Other studies have also found that patients with decreased BMD are more likely to experience an increase in lipid levels, develop more severe coronary atherosclerosis, and significantly increase the risk of stroke and myocardial infarction. Osteoporosis and atherosclerosis, the clinically significant consequences of which are, respectively, skeletal fractures and cardiovascular catastrophes, are the most common causes of a decrease in quality of life and an increase in mortality, especially in people over 50 years old. At the same time, the risk of osteoporotic fractures of the spine and/or femur and vascular complications associated with atherosclerosis increases sharply in this age group [12, 14].

Low BMD is an independent risk factor for cardiovascular mortality in older men and women, more important than blood pressure and cholesterol levels. In addition, menopause and estrogen deficiency, dietary habits, body weight, physical inactivity, smoking, hyperhomocysteinemia, oxidative stress, alcoholism, endocrine diseases also serve as risk factors for osteoporosis and atherosclerosis [18].

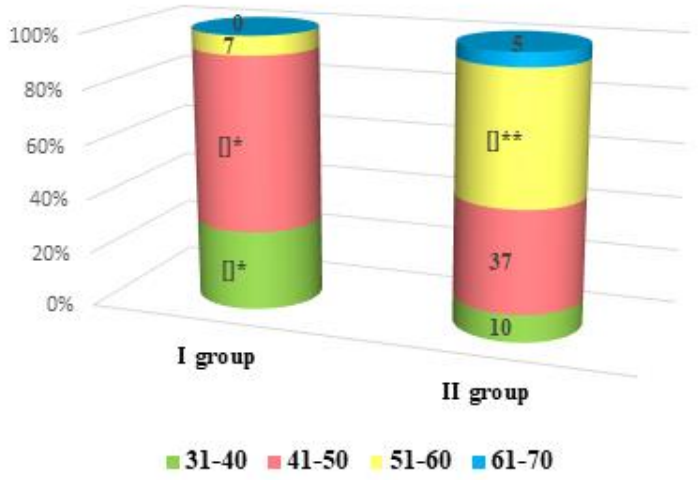
Pathophysiological basis of atherosclerosis and osteoporosis. The incidence increases with age, asymptomatic course of both diseases at the beginning of their development, high risk of CVD complications and fractures in post-menopausal women, common risk factors (smoking, low physical activity, estrogen deficiency). The basis of the diseases is a violation of calcium metabolism, unidirectional changes in hormonal systems regulating calcium metabolism, a number of drugs used to treat atherosclerosis are effective in maintaining bone mineral density. Drugs used to treat osteoporosis improve the condition of blood vessels [10]. Common processes occur in the main vessels, kidneys and bone tissue (Ca+deficient diseases), an imbalance in bone formation and resorption stimulates mineralization of the arterial wall and AK. Key markers of bone metabolism (osteocalcin, osteonectin, osteopontin, etc.) are involved in the development of atherosclerosis. Signs of ossification and development of cartilage in an atherosclerotic plaque. The role of monocytes (differentiation to “foamy” cells or osteoclasts), the relationship of oxidized LDL with osteoclast stimulation [2; 6].

Fractures of the vertebrae, proximal femur and distal forearm are most often observed in OP, however, fractures of other bones of the skeleton (ribs, sternum, pelvis, shin, humerus, etc.) may also occur [17; 19]. The identification of osteoporotic fractures in diseases associated with osteoporosis is an extremely important task, since their presence, on the one hand, affects the patient's quality of life, provoking chronic pain syndrome and impaired function of the musculoskeletal system, on the other hand, exacerbates irreversible damage in the body, increases the risk of repeated fractures, affects the prognosis of the underlying disease and the risks of premature death [10]. So, in a prospective two-year study V. Puisto, which included 3,730 women with vertebral fractures, mortality as a result of any injury was eight times higher (RR 0.89, 95% CI 0.60–1.31) than from common causes (RR 8.51 95% CI 3.48–20.77) [22]. In a retrospective study involving 97,142 patients with vertebral fractures, three-, five- and seven-year survival rates were 53.9, 30.9, and 10.5%, respectively. At the same time, mortality among patients with vertebral fractures was almost twice as high as in the control group, comparable in age, gender and race [20]. OP complicates the course of many rheumatic diseases. Most researchers associate its development in rheumatological patients with a chronic inflammatory process, impaired motor activity and exposure to medications, primarily with the intake of steroids [3; 15; 16].

The main instrumental method for the diagnosis of OP is the measurement of bone mineral density (BMD) during two-energy X-ray absorptiometry (DXA, densitometry) [27]. Densitometry makes it possible to predict the risk of fractures, including in the early stages, before the appearance of complications —

osteoporotic fractures, as well as to assess the dynamics of bone tissue, including monitoring the effectiveness of treatment. Screening for osteoporosis should be carried out in groups at risk of osteoporosis and fractures, primarily among postmenopausal women and men aged 50 years and older. Special attention should be paid to people who have suffered fractures with minimal trauma. Timely diagnosis of OP and adequate treatment will prevent them from having a "cascade" of fractures characteristic of OP. According to the WHO criteria for interpreting the results of densitometry in postmenopausal women and men 50 years and older, the diagnosis of OP is established with a decrease in BMD by 2.5 standard deviations from peak bone mass and below (the T-criterion is equal to or below -2.5 SD). However, the issue regarding the threshold value of BMD, at which initiation of anti-osteoporotic therapy of OP against the background of long-term therapy of steroids, has not yet been resolved. Thus, according to the European [21] and Russian recommendations on the STEROIDS OP [4], it is recommended to start treatment with a decrease in the value of the T-criterion to -1.5 SD and lower according to the results of densitometry in any part of the skeleton, whereas the American College of Rheumatology recommends the appointment of therapy with a value of the T-criterion of -1.0 SD [24]. It is known that fractures during HA therapy occur at higher BMD values than fractures in patients with postmenopausal OP. The results of various randomized clinical trials have shown that the incidence of fractures is higher in women receiving HA therapy, despite a younger age and higher BMD (T-criterion -1.2 standard deviation — CO) compared with women with postmenopausal OP (T-criterion from -2.4 to -2.8 CO), and with the same In terms of BMD, the risk of fractures in patients with steroids-OP is higher than in postmenopausal OP [26].

In order to determine the relationship between these two pathological conditions, we conducted studies in 105 patients with confirmed osteoporosis. The patients were in the arthrological department of the ROCKS and inpatient treatment in the departments of cardiorheumatology and cardiorheumatology of the multidisciplinary clinic of the Tashkent Medical Academy. For a prospective analysis, the patients were divided into two groups: Group I consisted of premenopausal women with OP (n=54). The 2nd group consisted of menopausal OP patients (n=51). 20 healthy volunteers were invited to the control group. They were almost the same age and gender as the OP patients. General clinical and biochemical blood tests, lipid spectrum, sex hormones Estradiol, FSH, LH were analyzed. Vascular endothelial growth factor (EGF), MXP-1 (monocyte chemoattractant protein-1) and nitric oxide were also studied among the indicators of endothelial dysfunction. Joints were also examined using RG, MRI and densitometry.



Note: *-p<0.01 is a significant difference compared to the indicators of group I; *- p<0.01 is a significant difference compared to the indicators of group II.

Figure 1. Distribution of the average age of pre- and postmenopausal women with OP by groups (%)

The percentage chart shows the distribution of patients with pre- and postmenopausal OP by average age. The majority of group I patients (64%) were aged 41-50 years. The smallest percentage of them (7%) were patients aged 51-60 years. On the contrary, representatives of group II in this age range had an advantage of 48%. The following places were occupied by (37%) 41-50-year-old patients and (5%) 61-70-year-old postmenopausal patients.

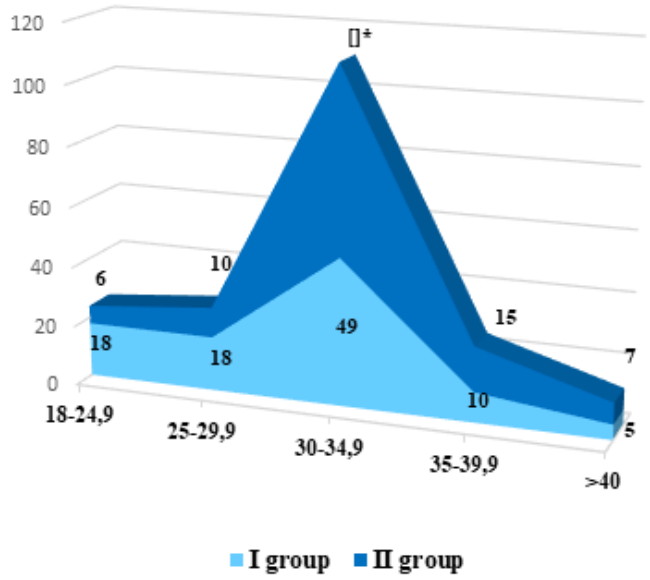
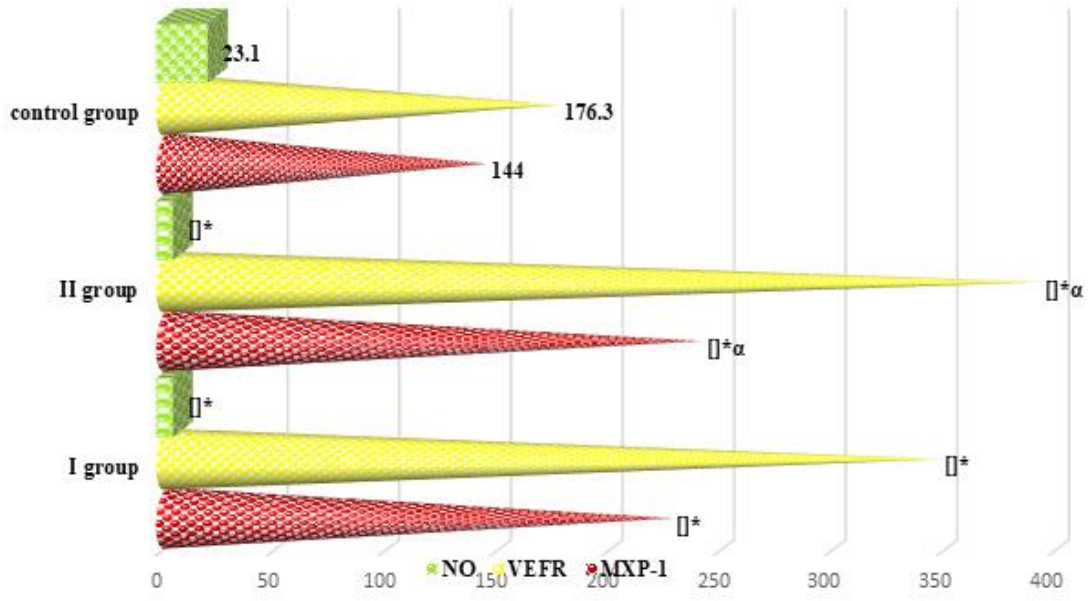


Figure 2. Body mass index in pre- and postmenopausal OP patients (%)

As shown in the figure on the right, postmenopausal patients had a higher body mass index (BMI) than premenopausal OP patients. In fact, we can observe that the level of obesity (BMI - 30-34.9) in women with OP in group II is statistically significantly higher than in patients of group I.

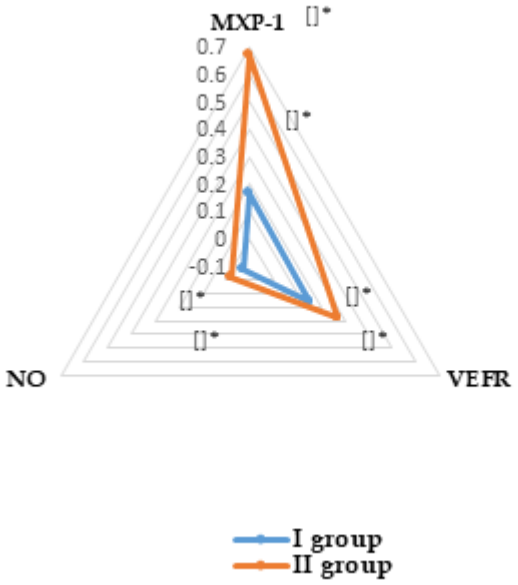


Note: *- p<0.001 is a significant difference compared to the indicators of the control group. α-p<0.5 is a significant difference compared to the indicators of group I.

Figure 3. Comparative analysis of the average amounts of MHP-1, VEFR and NO by group (iu/ml)

In order to assess endothelial dysfunction in menopausal OP patients, the indices of MHP-1, VEFR and NO were studied. As shown in Figure 3, it was found that the levels of MHP-1 and BFER were statistically significantly increased in patients of groups I and II in the pre- and postmenopausal period compared with the control group.

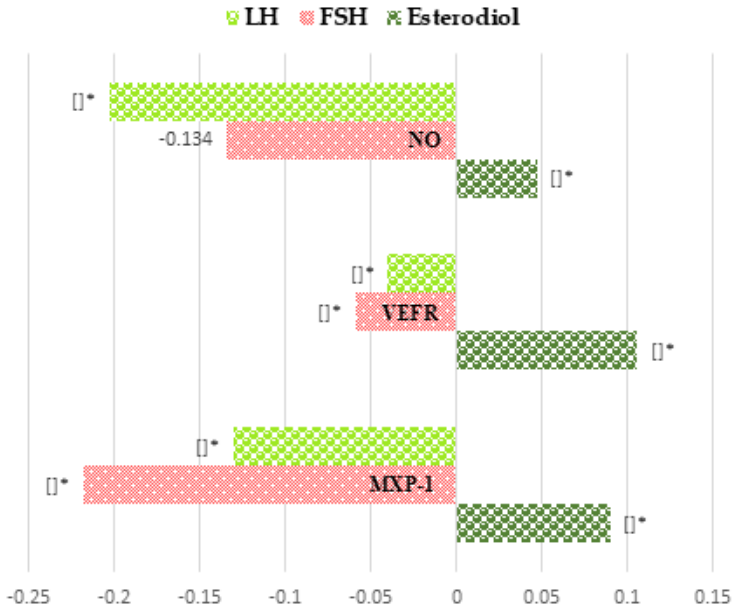
There were also diagnostically significant shifts between the NO titer groups. Indeed, it was noticed that the NO index in patients with OP decreased by almost three and a half times compared to the control group. Based on the situation described above, it is possible to draw a conclusion about the occurrence of endothelial dysfunction in patients with OP. When analyzing the changes in the sum of endothelial dysfunction indices between the groups, it was found that the titers of MHP-1 and VEFR were diagnostically significantly higher in postmenopausal patients than in premenopausal patients.



Note: *- p<0.01 is a significant difference from the compared indicators

Figure 4. Correlation between high BMI levels and indicators of endothelial dysfunction in premenopausal and postmenopausal women with osteoporosis

Figure 4 shows the correlation between higher IGE levels and indicators of endothelial dysfunction in postmenopausal women with OP. According to his data, a strong inverse correlation was revealed between the indicators of MHP-1 and VEF, overweight and obesity, as well as a strong inverse correlation with the titers of NO. A statistically significant advantage was observed in postmenopausal women of group II, who had a higher level of overweight and obesity than in premenopausal patients of group I, therefore, from the above situation it can be concluded that overweight and obesity enhance endothelial dysfunction, which directly affects the process of destruction in the joint, causes it degeneration.

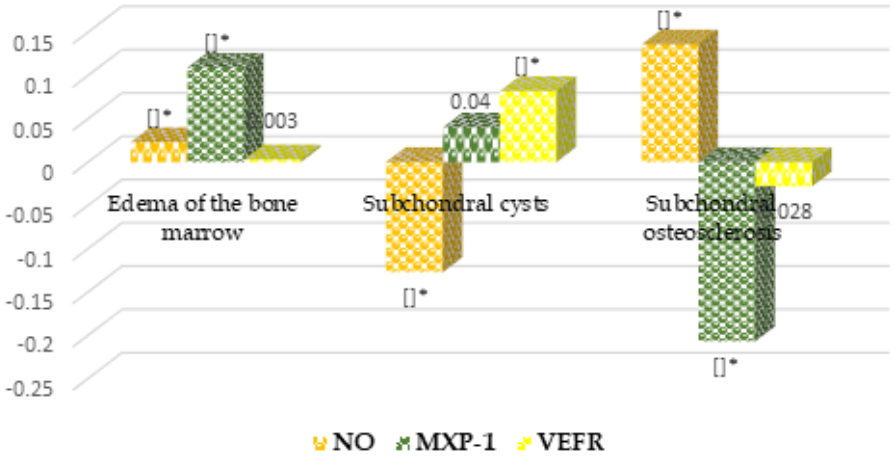


Note: *- p=0.05 is a significant difference in the compared indicators.

Figure 5. Correlation of indicators of endothelial dysfunction with the level of estradiol, FSH and LH in the blood of patients with osteoporosis

Figure 5 shows the correlation of estradiol, FSH and LH levels in the blood with markers of endothelial dysfunction in patients with OP. Based on the indicators of the presented diagram, a strong inverse correlation was established between serum estradiol and the titers of MHP-1, VEFR and NO. A correct correlation was observed between FSH and LH with the titers MHP-1, VEFR and NO.

The results presented on this slide (Figure 6) show a correlation between OP-specific parameters and the titers of MHP-1, VEFR and NO, determined during the MRI examination of patients. According to his data, a strong correct and reliable correlation was established between the level of edema of the bone marrow and subchondral cysts and the titers of MHP-1, VEFR and NO. An inverse correlation has been established between the signs of endothelial dysfunction and subchondral osteosclerosis, therefore, as endothelial dysfunction increases, the frequency of bone marrow tumors, subchondral cysts and osteosclerosis increases.



Note: *- p=0.169 is a significant difference compared to the compared indicators.

Figure 6. Correlation of MRI-determined parameters with MHP-1, VEFR and NO titers in patients with OP

Table 1. Indicators of dual-energy X-ray absorptiometry in peri- and postmenopausal women

Measuring area	All the patients		Perimenopausal patients		Postmenopausal patients		p*
	Median MPC by T criterion, SD (minimum, maximum)	Median MPC, g/cm2 (minimum, maximum)	Median MPC by T criterion, SD (minimum, maximum)	Median MPC, g/cm2 (minimum, maximum)	Median MPC by Criterion, SD (minimum, maximum)	Median MPC, g/cm2 (minimum, maximum)	
Hip neck	-0,8 (-3,4; 0,8)	0,793 (0,472; 0,986)	-0,3 (-1,2, 0,8)	0,836 (0,725; 0,986)	-1,5 (-3,4, 0,4)	0,714 (0,472; 0,941)	p = 0,0002
The overall hip index	-0,7 (-3,3; 0,9)	0,894 (0,569; 1,095)	-0,2 (-1,1, 0,9)	0,933 (0,829, 1,095)	-1,4 (-3,4, 0,5)	0,793 (0,569; 1,044)	p = 0,00000
L1–L4	-0,8 (-4,2; 1,3)	0,935 (0,114; 1,221)	-0,1 (-1,7, 1,2)	1,027 (0,814, 1,192)	-2,2 (-4,2, 1,3)	0,819 (0,623; 1,221)	p = 0,00000

*when comparing BMD in g/cm2 in peri- and postmenopausal women

As follows from the table, in the whole group, BMD indicators in the femoral neck were significantly lower than the total hip index (p = 0.000001) and in the spine (p = 0.000001). The values of BMD in the femoral neck (p = 0.0002), total hip index (p = 0.00000) and L1–L4 (p = 0.00000) among postmenopausal women were significantly lower than in premenopausal women.

Among all the surveyed 37 women (18.8%) had a T-test MPC of ≤ -2.5 SD, and 66 (33.5%) had a T-test MPC of ≤ -1.5 SD. At the same time, in the group of perimenopausal women, there were no patients with hip neck BMD and/or L1–L4, ≤ -2.5 SD according to the T-criterion, that is, those in the zone of osteoporosis. At the same time, every tenth patient (11.1%, n = 10) had BMD L1–L4 ≤ -1.5 SD according to the T-criterion. At the same time, there were no patients with hip neck BMD < -1.5 SD according to the T-criterion among the examined.

In the group of postmenopausal women, 39 women (45.3%) had hip BMD and/or L1–L4 indices corresponding to OP (≤ -2.5 SD according to the T criterion), 66 (76.7%) had hip BMD and/or L1–L4 indices were ≤ -1.5 SD according to T- criteria.

When comparing BMD in the femoral neck, with a common hip index and in the spine, no significant differences were found in women with early menopause and those in postmenopause (established in the usual time) (p> 0.05).

BMD in the femoral neck showed a moderate negative correlation with the duration of taking GCS (r = -0.4421, p = 0.000001), cumulative (r = -0.3542, p = 0.000001) and supportive (r = -0.3817, p = 0.000001) doses of GCS. A similar, but less pronounced correlation was noted in BMD in the overall hip index (r = -0.3675, p = 0.000001; r = -0.3147, p = 0.000001; r = -0.3869, p = 0.000001, respectively). At the same time, BMD in the spine was moderately correlated with the duration of GCS intake (r = -0.5261, p = 0.000001) and the cumulative dose (r = - 0.5434, p = 0.000001), but weakly with the maintenance dose of GCS (r = -0.2112, p = 0.0018).

Currently, there are effective programs for the prevention and treatment of OP, including a combination of non-pharmacological methods with modern anti-osteoporotic drugs [23].

Symptomatic: relief of acute pain (analgesics, local analgesics), removal of muscle spasm (muscle relaxants), calcium salts in accordance with age recommendations, physical therapy (individual regimen), physiotherapy (3-4 months after the start of pharmacotherapy) and wearing corsets.

Pathogenetic therapy of OP is drugs that slow down bone resorption: calcitonins, bisphosphonates (BF), estrogens, selective estrogen receptor modulators, calcium salts; drugs that stimulate bone formation: parathyroid hormone, anabolic steroids, growth hormone, androgens, fluorides; and drugs that have multifaceted effects on bone tissue and on both processes of bone remodeling (improving bone quality) [4; 18].

Currently, bisphosphonates (BP) are the first-line drugs for the treatment of OP, for which high therapeutic efficacy and satisfactory tolerability have been proven. Blocking the enzyme of the mevalonate pathway inside the osteoclast cell leads to the cessation of protein synthesis, which is important for the normal functioning of the osteoclast. As a result, cell function deteriorates, the life span of osteoclasts is shortened and, thus, the resorptive surface decreases and an antiresorptive effect is achieved. They also have a beneficial effect on the process of bone formation, on reducing the activity of osteoclasts, increasing bone formation, increasing BMD and increasing bone strength, as well as balancing bone metabolism.

Osteotropic minerals are involved in the synthesis of collagen in the bone matrix, which makes it possible to improve the quality of bone tissue when they are taken together with calcium [25; 28]. With the combined use of osteotropic minerals and calcium, there is a tendency to increase BMD by 1.28% per year. In the absence of treatment, BMD decreases by 2.23% per year. When taking only osteotropic minerals or calcium, the loss of BMD continues.

Vitamin D3 — cholecalciferol is formed in the malpighian and basal layer of the epidermis of the skin from 7-dehydrocholesterol (previtamin D) as a result of a non-enzymatic, UV-dependent photolysis reaction with a wavelength of 290-315 nm. The activity of the process is directly dependent on the intensity of irradiation and inversely on the degree of pigmentation of the skin. In the epidermis, cholecalciferol binds to vitamin D-binding protein and 70% of it from the bloodstream enters the liver, and the other part enters fat cells, where a vitamin D depot is formed. The main sources of Vitamin D2 (ergocalciferol) are fish, milk, as well as bread and mushrooms. Vitamin D2, which enters the body with food, is absorbed in the small intestine, necessarily in the presence of bile, then it is included in the composition of chylomicrons and transported by the lymphatic system into the venous bloodstream, then passing through the stages of metabolism similar to cholecalciferol. For its normal absorption, the presence of a sufficient amount of fat in food is necessary. Violation of bile secretion in diseases of the liver and biliary tract significantly impedes the absorption of vitamin in the intestine.

Due to the presented scientific data, which are widely presented in the literature, a number of issues related to the careful monitoring of irreversible injuries, including osteoporosis and compression fractures of the vertebrae, especially in peri- and postmenopausal women, remain unresolved in full. This was the basis for this study.

Objective: to study the efficacy and tolerability of the drug Forcal plus in osteopenia in postmenopausal women. 80 women aged 45 to 65 years were divided into 2 groups:

Group 1 – received Forcal plus (1 tablet 2 times a day)

Group 2 – did not receive treatment (control)

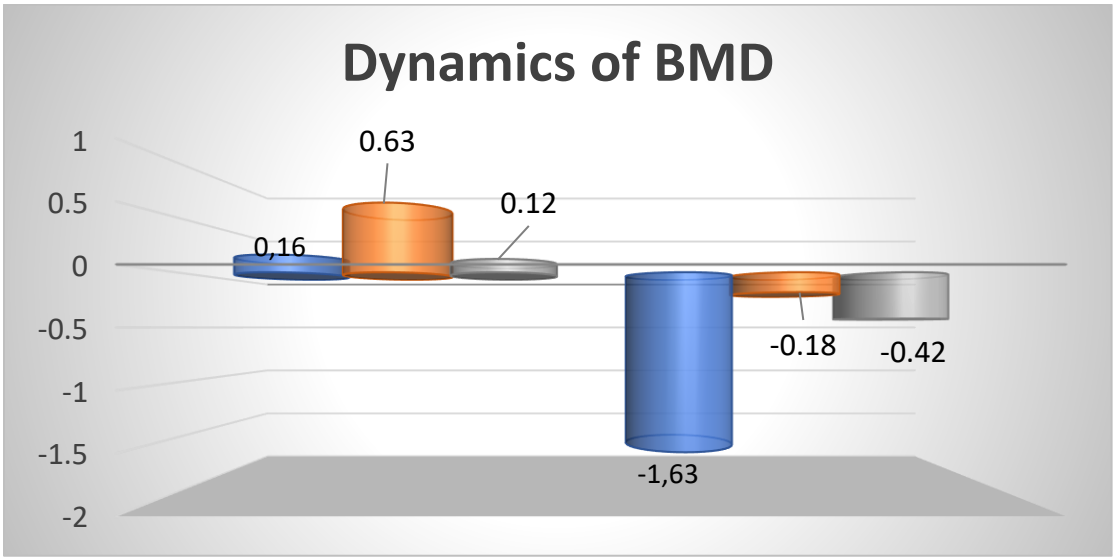


Figure 7. Dynamics of BMD in the complex treatment of postmenopausal osteoporosis

Combination therapy in both groups is significantly effective in its effect on BMD L1-L4. Therapy using Forcal plus showed a significantly greater increase in BMD in the vertebrae. There was a significantly greater decrease in pain syndrome.

Thus, MCP-1 and VEGF titers were higher in postmenopausal women compared with premenopausal patients, and NO titers were statistically significantly lower in menopausal osteoporosis patients, changes in the amount of estradiol, FSH and LH in blood serum depend on the level of clinical and laboratory activity of the disease and systemic degenerative changes in the body Similarly, postmenopause, long-term intake and high doses of HA are important factors in reducing BMD in women with OA, which is more pronounced in the hip. Therapy using Forcal plus showed a significantly greater increase in BMD in the vertebrae. There was a significantly greater decrease in pain syndrome.

In conclusion, it should be noted that Forcal plus is an effective means of OP therapy. Its long-term use in the complex therapy of various forms of OP leads not only to a progressive increase in BMD in the lumbar spine and proximal femur, but also to a decrease in the risk of vertebral fractures.

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