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THERAPY WITH VITAMIN D METABOLITS OF STRUCTURAL AND FUNCTIONAL CHANGES IN BONE TISSUE OF WORKING POSTMENOPAUSAL WOMEN WITH OSTEARCOPENIA

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Abstract

The prevalence of osteoporosis and vitamin D deficiency in postmenopausal women working under harmful labour conditions has been examined. Reduced bone mineral density was revealed in 85% of the persons under observation, the incidence of OP was 35%, sarcopenia (SP) - 35%. Vitamin D deficiency was found in 91.3% of the workers, at the same time severe VD deficiency was observed in 32.9%, VD deficiency - in 7.5%, and the optimal level of vitamin D was observed in 1.2% of cases. 79 PM women with OP aged 50 - 60 y. o. (mean age - (55.7 ± 0.9) years), working at harmful conditions of the working environment with an average length of service 26.14 ± 0.91 years have been examined. Clinical group A (n = 30) received *cholecalciferol* at a dose of 2000 IU (4 drops) per day and *alfacalcidol* 1 μg (1 capsule) once a day for a year. This resulted in a positive effect on the level of 25(OH)D. The complex appointment of *cholecalciferol* and *alfacalcidol* reduced the level of PTH and confirmed the role of VD deficiency in the progress of secondary hyperparathyroidism. The data obtained revealed a slowing of the effect of VD on osteoclastogenesis. Decrease of bone resorption marker CTx in the women under examination confirmed the latter.

Key words: postmenopausal woman; harmful labour conditions; bone mineral density; vitamin D metabolit.

Healthy aging is a new global strategy of the World Health Organization aimed to reduce morbidity, maintain vitality and well-being in old age (WHO, 2016). According to the Centers for Disease Control (CDC, USA), sarcopenia (SP) is recognized as one of the five major risk factors for morbidity, disability, loss of independence, deteriorating quality of life and mortality in people over 65 [1, 2, 3].

The combination of SP and osteoporosis (OP) doubles the risk of fractures and premature death in patients [4]

The development of SP was observed in 50% of women with postmenopausal OP and in 25% of osteopenia women in postmenopause [5, 6].

The development of postmenopausal osteosarcopenia (OSP) is due to genetic factors, body composition changes, low physical activity, estrogen and vitamin D deficiency and leads to muscle mass, strength, functionality decrease, which in combination with comorbidity is realized by increased fracture frequency, mortality [7].

Numerous studies have emphasized the role of vitamin D metabolites in the correction of structural and functional disorders of the skeletal and musculoskeletal system in postmenopause [8 - 11].

To maintain an active lifestyle allows to reduce further loss of bone and musculoskeletal mass, eliminate the risk of deep vein thrombosis, cardiovascular complications, lung disease and, consequently, to prolong life in this group of patients.

Literature data show that 30% of a worker's health depends on working conditions [12-15].

It has been proven that work under harmful conditions contributes to the earlier onset of menopause. Harmful factors of production act as a provoking and modifying factor, catalyst for natural involutive processes and lead to premature aging of organs and systems, including the musculoskeletal system (MSS).

Therefore, it is important to develop a scheme of comprehensive treatment and rehabilitation measures aimed to improve the functionality of the musculoskeletal system and prevent postural disorders in postmenopausal women with osteosarcopenia working under adverse factors of the working environment. This is of strategic importance to prevent the risk of occupational injuries, disability and disability. All of the above determines the scientific, practical and social significance of this work.

The purpose. To study the frequency of vitamin D deficiency, the effect of vitamin D on structural and functional changes in bone and muscle tissue in postmenopausal women with OSP working under harmful factors of the working environment.

Materials and methods

79 PM women aged 50 - 60 y.o. (mean age - (55.7 ± 0.9) years) with OP, who worked under harmful industrial conditions were examined. Their average length of service was (26.14 ± 0.91) years.

Assessment of phosphorus-calcium metabolism was performed by determining in blood serum: total calcium - colorimetric method on the analyzer Cobas 6000 (Roche Diagnostics, Switzerland), ionized calcium - ion-selective method, analyzer ABL 9180 (RocheDiagnostics), phosphorus – spectrophotometric method, Cobas 6000 (Roche Diagnostics, Switzerland), PTH - immunochemiluminescent method "ECLIA", e Cobas 6000 analyzer (Roche Diagnostics, Switzerland).

Serum level of 25 (OH) D was determined by enzyme-linked immunosorbent assay on the EUROIMMUN analyzer (Germany). The level of bone tissue resorption marker B-Cross Laps - C-terminal telopeptide, type I collagen degradation product (CTx) and marker of bone tissue formation. PTH in serum was determined by immunochemiluminescent method "ECLIA" on a Cobas 6000 analyzer (Roche Diagnostics, Switzerland);

Level of OPG - by enzyme-linked immunosorbent assay on "AxsymSystem" (Abbot, Germany).

Assessment of BMD was also performed by X-ray densitometry (osteodensitometer Hologic Discovery, USA).

Statistical processing of the data obtained data was performed using Microsoft Office Excel and Statistica 6.0 applications. For mathematical processing, the methods of primary descriptive statistics were used: mean value, standard deviation, standard error, Student's t-test for related samples, one-sample Wilcoxon test and one-way analysis of variance (ANOVA). The correlation analysis of the indicators under study was carried out on the basis of calculation of paired Spearman correlation coefficients. The Chaddock scale (analysis of the strength of the relationship between variables) was used to estimate the strength of the correlation coefficients. The next step was to build a model in the form of linear one-factor linear regression and multiple regression. Methods of system analysis were used to assess the effectiveness of treatment. Indicators (criteria) of effectiveness of treatment which allow to objectively compare different treatment methods have been developed.

Results and discussion

The prevalence of OP and vitamin D deficiency (VD D) in PM women working under harmful industrial conditions has been analyzed. Reduced BMD was observed in 85% of the persons under examination, the incidence of OP equals to 35%, SP - 35% in all OP women. Vitamin D deficiency was found in 91.3% of the examinees, including severe deficiency - in 32.9% of observations, vitamin D deficiency was revealed in 7.5% of cases. Only 1.2% of the patients under examination had the optimal level of vitamin D (OVD).

The examinees were divided into 3 clinical groups:

- clinical group A (n = 30) got cholecalciferol at a dose of 2000 IU (4 drops) per day and alfacalcidol 1 μg (1 capsule) once per day during a year;

- clinical group B (n = 30) - cholecalciferol at a dose of 2000 IU (4 drops) per day during a year;

- control group K (n = 15) - did not receive vitamin D metabolites.

Prior to the treatment, the structural and functional state of bone tissue was compared in all groups under study.

25 (OH) D level in all groups gave evidence of VD D and did not differ statistically, e.g. in group A it was (15.14 ± 1.96) ng / ml, in group B - (15.06 ± 1.69) ng / ml , in group K - (15.56 ± 1.85) ng / ml ($p > 0.05$).

In group A the PTH level was (42.84 ± 4.59) pg / ml, in group B - (43.07 ± 4.39) ng / ml, in group K - (41.19 ± 3.39) ng / ml ($p > 0.05$), correspondingly.

Indicators of phosphorus-calcium metabolism also did not differ statistically ($p > 0.05$). Thus, total calcium in group A equals to (2.39 ± 0.04) mmol / l, in group B - (2.39 ± 0, 05) mmol / l, in the control group - (2.40 ± 0.04) mmol / l; calcium ionized level in group A constituted (1.24 ± 0.01) mmol / l, in group B - (1.29 ± 0.02) mmol / l, in the control group - (1.28 ± 0.02) mmol / l; phosphorus level in group A was (1.05 ± 0.02) mmol / l, in group B - (1.05 ± 0.03) mmol / l, in control group - (1.04 ± 0.04) mmol / l.

CTx in group A was (0.684 ± 0.148) mmol / l, in group B - (0.665 ± 0.134) mmol / l, in the control group - (0.659 ± 0.146) mmol / l ($p > 0.05$). The marker of bone formation OC was not statistically different and was (13.31 ± 2.51) ng / ml in group A, in group B - (13.90 ± 2.44) ng / ml, in the control group - (13.74 ± 1.88) ng / ml ($p > 0.05$).

OPG level was reduced in the groups under study and statistically ($p > 0.05$) did not differ.

In group A it was (1.42 ± 0.19) pmol / l, in group B - (1.48 ± 0.19) pmol / l, in the control group - (1.46 ± 0.19) pmol / l. The indicators of BMD, according to the T-test, were

reduced and amounted to (-2.34 ± 0.52) SD in group A, in group B - (-2.28 ± 0.48) SD, in the control group - (-2.29 ± 0.5) SD.

The level of 25 (OH) D was determined before treatment, and in 3, 6 and 12 months. The seasonal factor was not taken into account due to the peculiarities of the labor process. After the correction made, there was an increase in the level of 25 (OH) D in groups A and B (p <0,05). Increase of 25 (OH) D was 34.6% (from (15.14 ± 1.96) to (25.85 ± 1.41) ng / ml (p <0.05)) in 3 months in group A, in group B - 30.2 % (from (15.06 ± 1.69) (24.91 ± 1.28) ng / ml (p <0.05)), in the control group the value of the indicator did not change (from 15.56 ± 1, 85) to (15.99 ± 1.81) ng / ml (p> 0.05)). In 6 months its increase in group A averaged 49.6% (from (15.14 ± 1.96) to (34.79 ± 1.65) ng / ml (p <0.05)), in group B - 39, 9% (from (15.06 ± 1.69) to (32.43 ± 1.72) ng / ml (p <0.05)), in the control group the value of the indicator did not change significantly (from (15.56 ± 1.85) to (16.21 ± 1.7) ng / ml (p> 0.05)). In 12 months the increase in group A was 155.4% (from (15.14 ± 1.96) to (38.66 ± 1.51) ng / ml (p <0.05)), in group B - 131.7% (from (15.06 ± 1.69) to (34.86 ± 1.33) ng / ml (p <0.05)), in the control group the value of the indicator did not change significantly (from (15.56 ± 1, 85) to (16.07 ± 1.54) ng / ml (p> 0.05)), (Fig. 1).

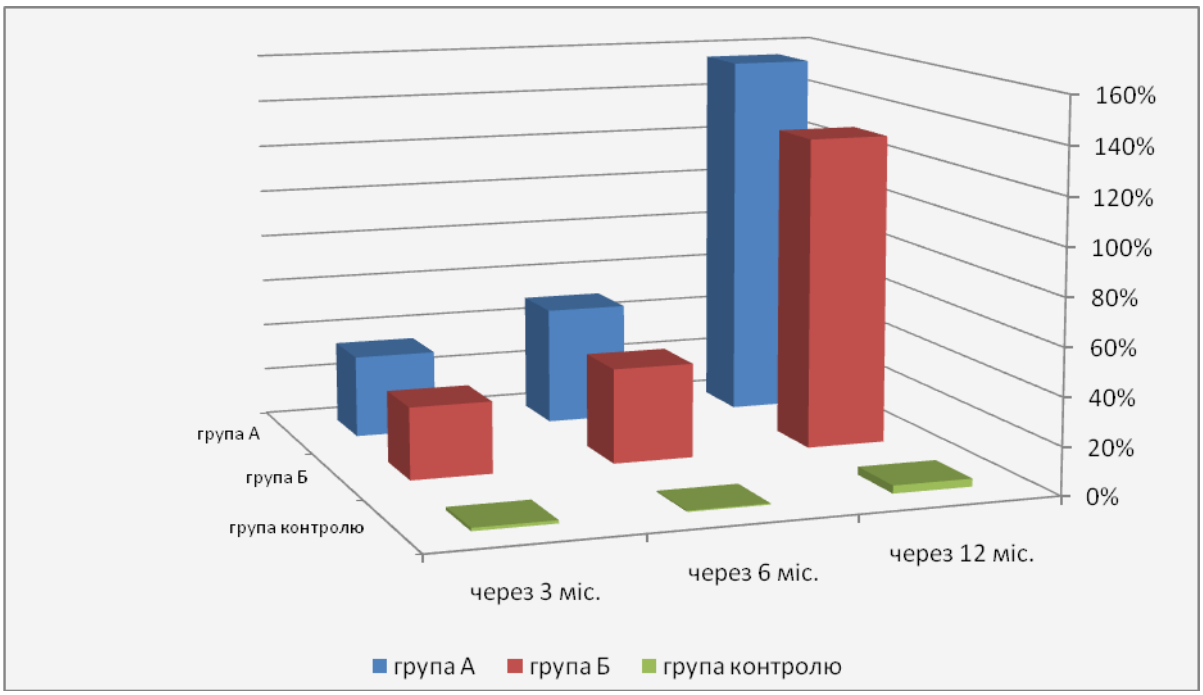

Fig. 1. The increase in 25-hydroxyvitamin D in 3, 6 and 12 months in low bone mineral density women, %

The results ontained indicate a positive effect of cholecalciferol and alfacalcidol on the level of 25 (OH) D in the groups unders tudy. The most significant increase was observed in clinical group A due to the synergistic effect of cholecalciferol and alfacalcidol (p <0.05).

Analysis of PTH showed a tendency to its decrease in groups A and B. Decrease in PTH in 6 months in group A averaged 11.65% (from (42.84 ± 4.59) to (37.85 ± 2.81) pg / ml (p <0.05)), in group B - 10.06 % (from (43.07 ± 4.39) to (38.73 ± 2.32) pg / ml (p <0.05)), in the control group the value of the indicator decreased by 3.71% (from (41, 19 ± 3.39) to (39.66 ± 3.32) pg / ml) and had no statistical significance (p> 0.05). In 12 months reduction of PTH in group A averaged 17.46% (from (42.84 ± 4.59) to (35.36 ± 2.03) pg / ml (p <0.05)), in group B - 15, 73% (from (43.07 ± 4.39) to (36.29 ± 2.15) pg / ml (p <0.05)), in the control group - 4.89% (from (41.19 ± 3.39) to (39.17 ± 2.98) pg / ml (p> 0.05)), (Fig. 2).

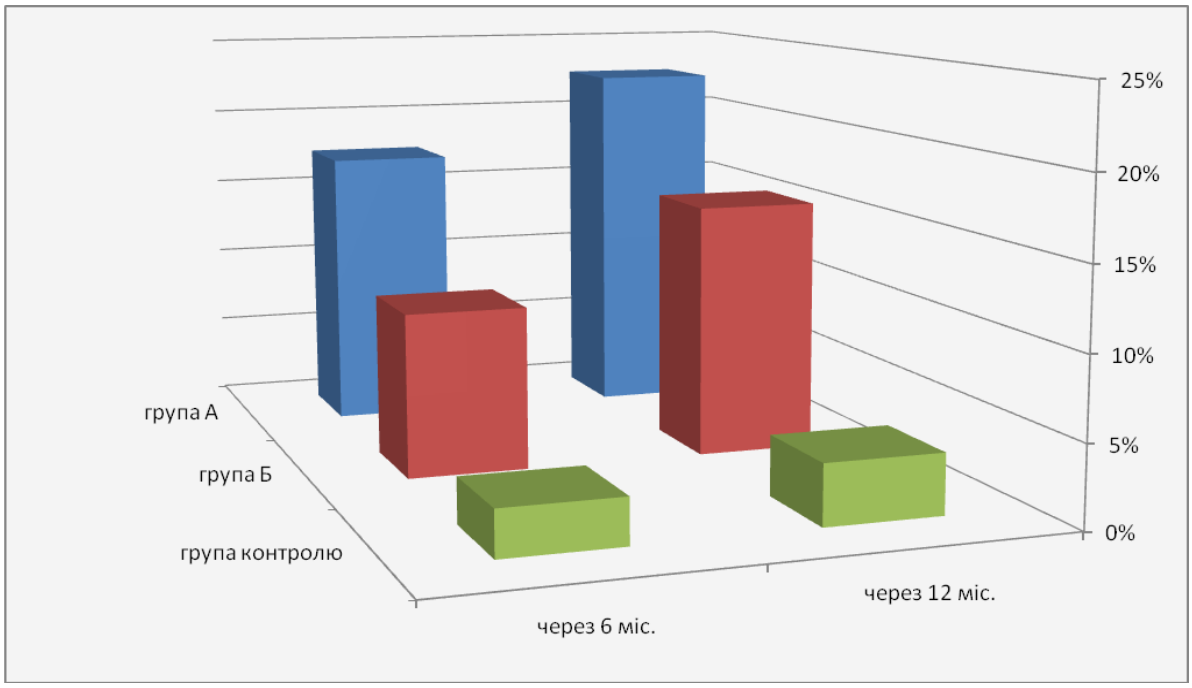

Fig. 2. Changes in parathyroid hormone levels inr 6 and 12 months in low bone mineral density womwn, %

Thus, the complex administration of cholecalciferol and alfacalcidol helps to reduce the level of PTH and confirms the role of VD D in the development of secondary hyperparathyroidism.

Analysis of the marker of bone resorption on the background of the treatment showed a decrease in CTx in groups A and B. Decrease in CTx in 6 months in group A was 22.1%

(from (0.684 ± 0.148) to (0.533 ± 0.088) ng / ml (p<0.05)), in group B - 9.2% (from (0.665 ± 0.134) to (0.604 ± 0.128) ng / ml (p<0.05)).

In 12 months. in group A a decrease of 30.7% (from 0.684 ± 0.148) to (0.474 ± 0.072) ng / ml (p<0.05) was recorded, in group B - by 15.3% (from 0.665 ± 0.134)) to (0.563 ± 0.122) ng / ml (p<0.05)). In the control group women there was an increase in the CTx marker by 3.8% in 6 months (from 0.659 ± 0.146) to (0.684 ± 0.144) ng / ml (p <0.05)) and by 8% in 12 months. (from (0.659 ± 0.146) to (0.712 ± 0.152) ng / ml (p <0.05)), (Fig. 3).

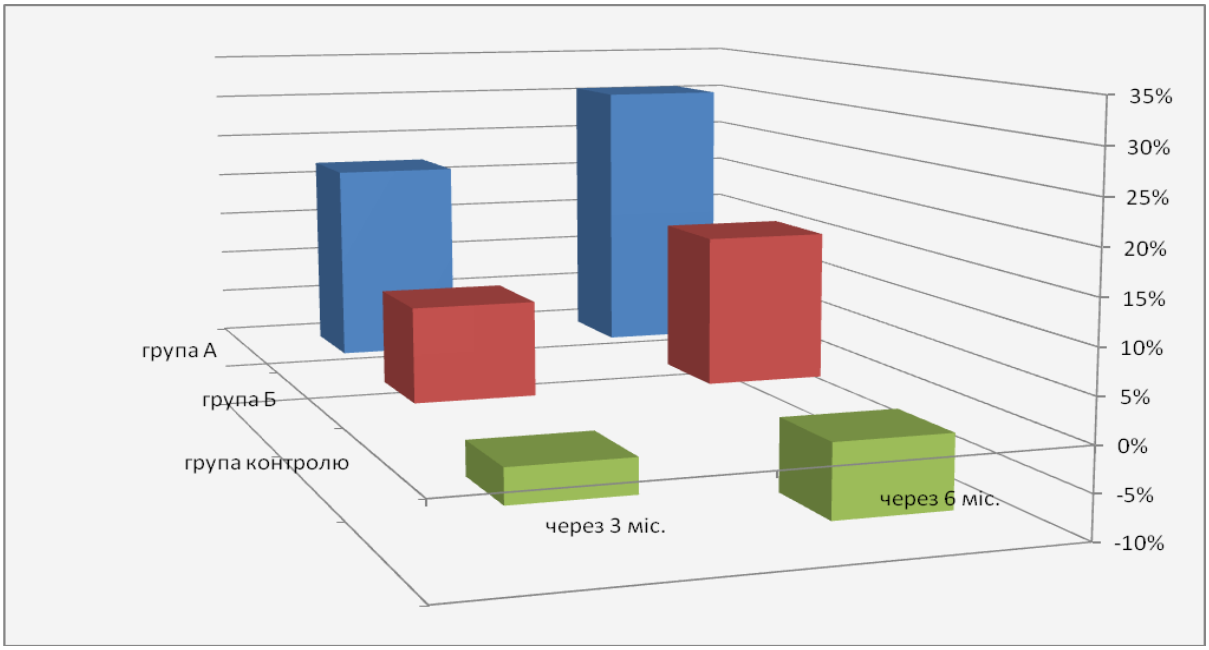

Fig. 3. Changes in C-telopeptidecollagen type I in 6 and 12 months in low bone mineral density womwn, %

The data obtained show a slowing of the effect of vitamin D on osteoclastogenesis, which is confirmed by a decrease in the level of markers of bone resorption CTx in women of groups A and B. Moreover, statistically significant (p <0.05) antiresorptive effect was revealed at the administration of double-component therapy, i.e. cholecalciferol and alfacalcidol. An increase of CT_X level in women of the control group indicates an acceleration of the resorption of bone tissue.

Increase in the marker of bone tissue formation OC in 6 months in group A averaged 12.9% (from 13.31 ± 2.51) to (15.04 ± 2.01) ng / ml (p <0.05)), in group B - 3.7 % (from (13.90 ± 2.24) to (14.41 ± 2.25) ng / ml (p <0.05)), in the control group - 1.6% (from (13.74 ± 1) , 88) to (13.91 ± 1.60) ng / ml (p> 0.05)). In 12 months its increase in group A averaged 20.9% (from 13.31 ± 2.51) to (16.11 ± 1.86) ng / ml (p <0.05)), in group B - 7, 6% (from

(13.90 ± 2.24) to (14.96 ± 2.07) ng / ml (p <0.05)), in the control group it decreased by 0.5% (from (13.74 ± 2.07) ± 1.88) to (13.67 ± 1.58) ng / ml (p> 0.05)), (Fig. 4).

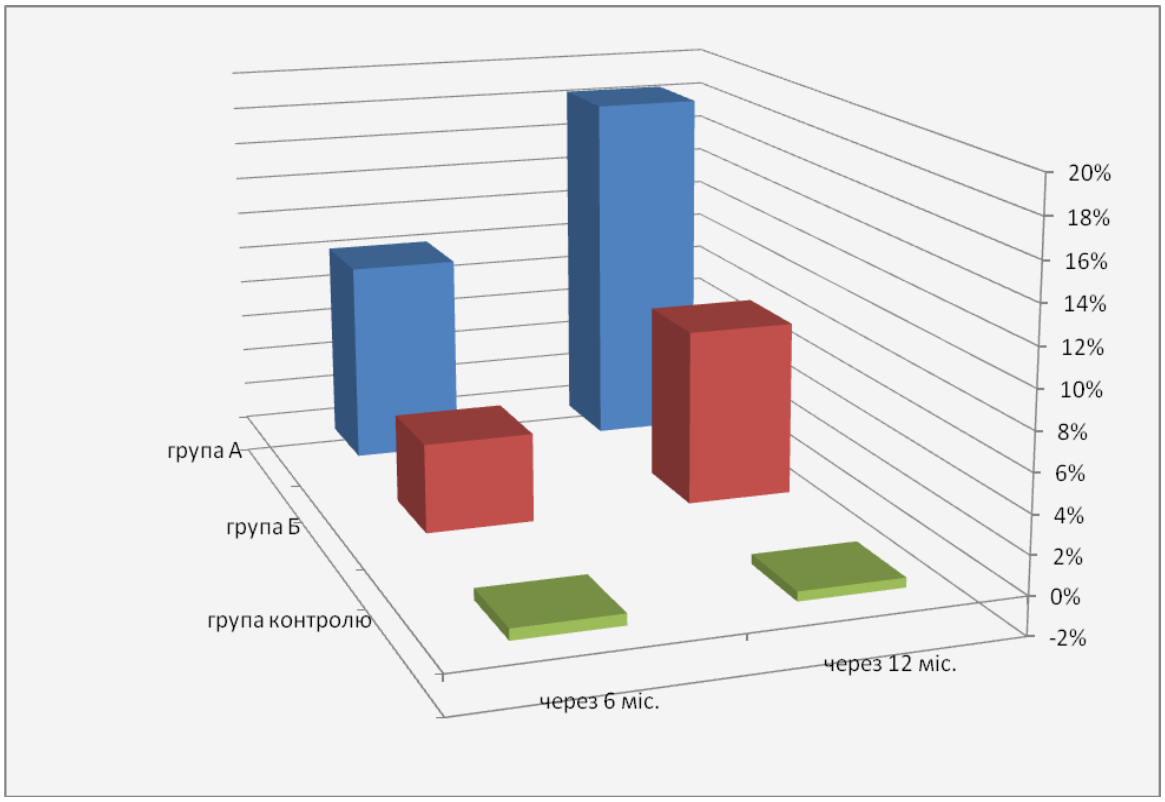

Fig. 4. Increase in osteocalcin inr 6 and 12 months in low bone mineral density womwn, %

Against the background of VD D and HBD correction in women of groups A and B a significant increase (p <0.05) in the average level of OC was revealed. But its marked increase was observed in group A. This indicates a positive effect of combination therapy with vitamin D on bone formation. A slight increase in the level of OC in group B demonstrates a slowdown in bone formation on the background of monotherapy with cholecalciferol. No OC increase in 6 months and its negative dynamics in 12 months indicates the imperfection of bone formation in women with hypertension and obesity and the presence of VD D and HBD in them.

OPG increase in 6 months. in group A averaged 67.4% (from 1.42 ± 0.19) to (2.37 ± 0.17) pmol / l (p <0.05)), in group B - 24.9 % (from (1.48 ± 0.19) to (1.85 ± 0.17) pmol / l (p <0.05)). In 12 months the increase in group A averaged 120.2% (from (1.42 ± 0.19) to (3.12 ± 0.16) pmol / l (p <0.05)), in group B - 52, 5% (from 1.48 ± 0.19) to (2.26 ± 0.18) pmol / l (p <0.05)), in the control group the values of the indicator, respectively, were from a decrease of

0.58% from (1.46 ± 0.19) to (1.45 ± 0.18) pmol / l (p> 0.05)) to an increase of 0.9% (from (1.46 ± 0.19) to (1.47 ± 0.18) pmol / l (p> 0.05)), ie did not change (Fig. 5).

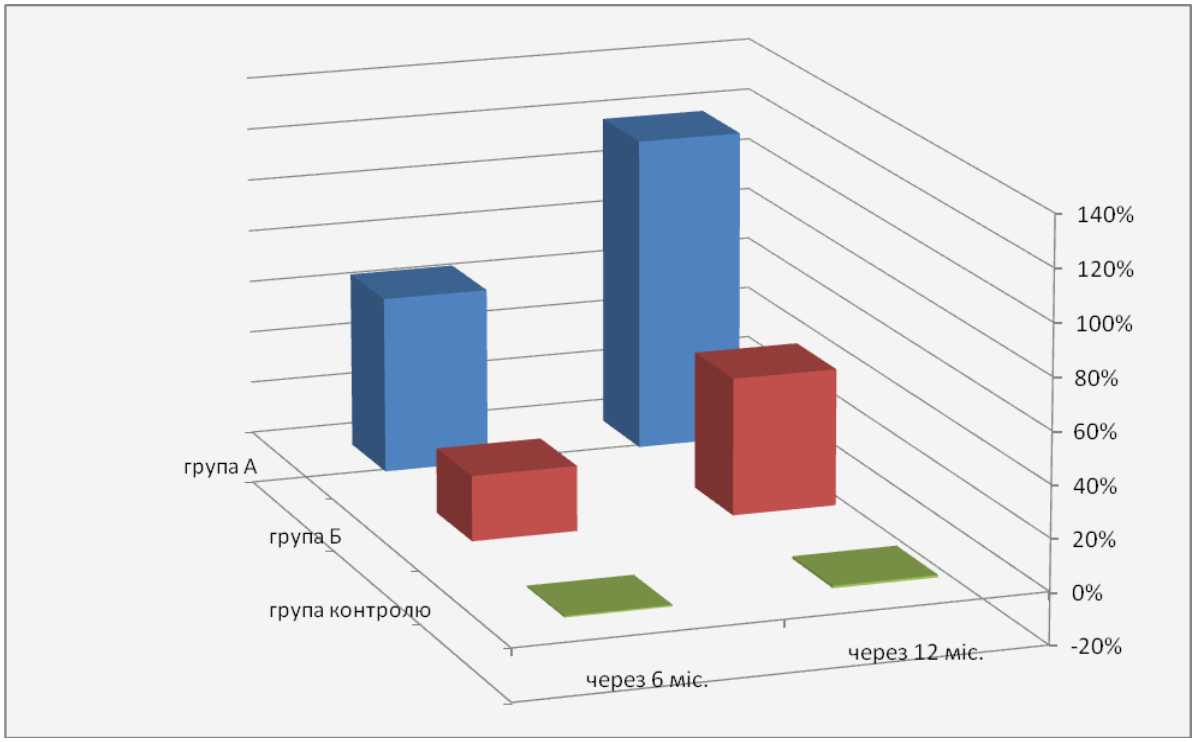

Fig. 5. Increase in osteoprotegerin content in 6 and 12 months in low bone mineral density women, %.

The results obtained confirm the role of vitamin D in the regulation of OPG production and secretion and indicate the effectiveness of vitamin D in OPG levels correction, and a more pronounced increase is facilitated by two-component therapy with cholecalciferol in combination with alfacalcidol (p <0.001).

Increase in T-test in 6 months in group A averaged 2.1% (from (2.34 ± 0.52) to (-2.29 ± 0.44) SD (p <0.05)), in group B - 0.9% (from (-2.28 ± 0.48) to (-2.26 ± 0.47) SD (p <0.05)). In 12 months the increase in group A averaged 3.8% (from (-2.34 ± 0.52) to (-2.25 ± 0.41) SD (p <0.05)), in group B - 2, 2% (from (-2.28 ± 0.48) to (-2.23 ± 0.5) SD (p <0.05)).

In the control group there was a decrease in BMD. T-test indexes in 6 months decreased by 1.7% (from (-2.29 ± 0.56) to (-2.33 ± 0.55) SD (p <0.05)), in 12 months - by 3.5% (from (-2.29 ± 0.56) to (-2.37 ± 0.56) SD (p <0.05)), (Fig. 6).

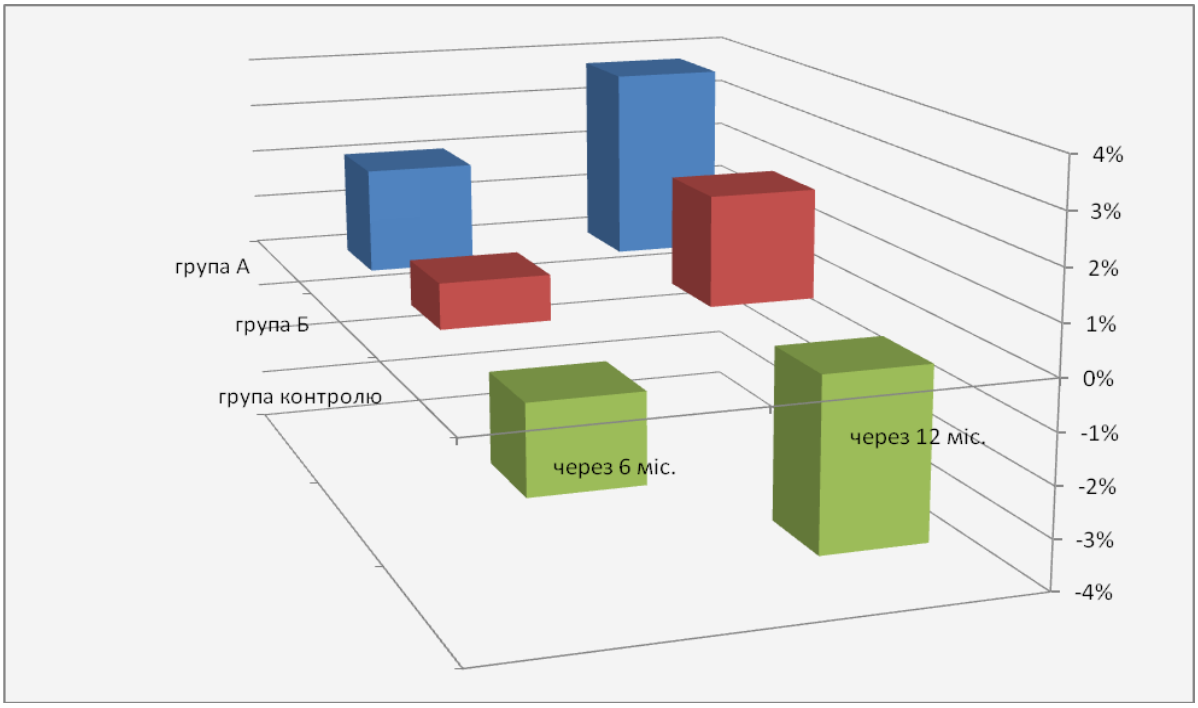

Fig. 6. Increase in bone mineral density (according to the T-test) in 6 and 12 months in low bone mineral density women, %

During the entire course of treatment in the examined women there was no significant increase in total and ionized calcium ($p > 0.05$) in serum, which was regarded as safety in prescribing the claimed combination of vitamin D. Tests to assess the functional state of the muscular system also indicate significant ($p < 0,001$) improvement in muscle function during therapy.

Conclusions

The data obtained indicate that vitamin D preparations, which are used to correct its deficiency and HBD in OP women have a positive therapeutic effect on the state of bone tissue, which is reflected in BMD growth. A statistically significant effect was observed under combined administration of cholecalciferol and alfacalcidol ($p<0.05$). The absence or insufficient correction of VD D and HBD contributes to the progressive reduction of BMD ($p<0.05$).

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