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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

**THE ROLE OF PROTEIN AND PEPTIDE REGULATORS IN
BONE AND CARTILAGE METABOLISM IN PATIENTS
WITH OSTEOPOROSIS ACCOMPANIED BY FRACTURE**

Speciality: 2406.02 – Biochemistry

Field of science: Medicine

Applicant: **Naila Arif Hasanova**

Baku – 2023

The work was performed at Clinical-diagnostic laboratory of the Scientific Research Institute of Traumatology and Orthopedics and at the Scientific Research laboratory of the Department of Biological Chemistry of the Azerbaijan Medical University.

Scientific supervisor: Doctor of Biological Sciences, Professor
Gulnara Ibrahim Azizova

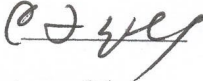
Scientific consultant: Doctor of Medical Sciences, Professor
Galandar Surkhay Janbakhishov

Official opponents: Professor, Doctor
Abdurrahim Kocyigit


Doctor of Philosophy in Medicine
Mirshahin Azizagha Musayev

Doctor of Philosophy in Medicine
Ogtay Sabir Abdullayev

Dissertation council FD 2.07 of the Supreme Attestation Commission under the President of the Republic of Azerbaijan operating at the Azerbaijan Medical University

Chairman of the Dissertation Council: Honored Scientist,
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Sabir Jahan Aliyev

Scientific secretary of the Dissertation Council: 
Doctor of Philosophy in Biological Sciences, Associate Professor
Agil Hasan Orujov

Chairman of the Scientific Seminar: 
Doctor of Biological Sciences,
Namig Oruj Gudratov



İMZANI TƏSDİQ EDİRƏM
Azərbaycan Tibb Universitetinin
ELMI KATIBI
Tibb elmləri doktoru, professor
Nazim Adil oğlu Pənahov
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GENERAL CHARACTERISTICS OF THE RESEARCH

Relevance of the topic and degree of the research.

Osteoporosis is one of the serious and global health problems. Fractures caused by osteoporosis lead to loss of the working ability of the people^{1,2}. Osteoporosis (Greek: osteo - bone, poros - hole) is a chronic developing system and metabolic disease of the skeleton, caused by a decrease in bone mass, microarchitecture disruption, and bone fragility. Deformations and fractures of bones are observed as a result of damage to bone tissue and a decrease in its density^{3,4}.

Osteoporosis is a very common disease, especially in women during menopause. According to the World Health Organization (WHO), the disease is the fourth most common non-communicable disease after cardiovascular, oncological, and diabetes diseases. According to statistics, osteoporosis is found in one out of three women and one out of five men in the world after the age of 50. According to 2020 statistics, 71% of the population over 70 years old suffers from osteoporosis. Osteoporosis is one of the main causes of disability and death of elderly people in the world. Every year in the world 9 mln. new fractures due to osteoporosis are reported, of which 1.6 million are femur fractures. For the Caucasian population, the lifetime risk of fractures after age 50 is 45-55% for women and 14-22% for men. Usually, fractures occur in the femoral neck, spinal column, sacrum, wrist bones, and rarely in other bones^{5,6,7,8}.

¹ Положаева, И.В., Алиякпаров М.Т. Актуальность проблемы остеопороза в молодом возрасте и его ранней современной диагностики // Международный журнал прикладных и фундаментальных исследований, – 2018. № 2, – с.115-120.

² Дудинская, Е.Н. Остеопороз у пожилых пациентов / Е.Н.Дудинская, Н.В.Браилова, В.А.Кузнецова [и др.] // Остеопороз и остеопатии, – 2019. № 22(3), – с.34-40.

³ Əliyeva, N.N. Osteoporoz. Sümük toxumasının generalizə olunmuş itirilməsinin patofiziologiyası // – Bakı: Azərbaycan Tibb Jurnalı, – 2008. № 3, s.153-156.

⁴ Kışlak, P., Fatma Genç. Osteoporoz ve tedavisi // Lectio Scientific Journal of Health and Natural Sciences – 2019. July, Volume 3, Issue 1, – p. 1-18.

⁵ Blackie, R. Diagnosis, assessment and management of osteoporosis. // Prescriber, –2020. 31, – p.14-19.

Since there are some difficulties in making a timely diagnosis with the current diagnostic methods, the identification of new and more informative biochemical markers reflecting metabolic processes in bone tissue may be of great scientific and practical importance. Until now, many biochemical indicators have been determined in the laboratory diagnosis of osteoporosis. The study of new biochemical indicators is necessary due to the lack of deep knowledge of bone and cartilage metabolism during osteoporotic fractures, the insufficiency of diagnostic parameters, and the fact that biomarkers of prognostic significance during the recovery process are less informative.

In the processes of bone formation, resorption, and remodeling, a number of components of bone metabolism - bone biomarkers - are released. In the last 10 years, these markers have attracted great attention in the diagnosis of osteoporosis, assessing the degree of severity, predicting the risk of fractures including, the clinical evaluation of the treatment.

Modern diagnosis of osteoporosis is based on the determination of a wide range of biomarkers (products of bone and cartilage metabolism, vitamin D, etc.) along with instrumental examination methods⁹. In recent years, special attention has been paid to the study of protein and peptide regulators, which play an important role in the pathogenetic mechanisms of osteoporosis, and to the determination of their diagnostic and prognostic possibilities. The role of protein and peptide biomarkers such as cartilage glycoprotein-39 (HCgp39, YKL-40), osteoactivin (GPNMB) and

⁶ Sotornik, I. Osteoporosis – epidemiology and pathogenesis // *Vnitr Lek.*, – 2016. vol. 62, – p.84-87;

⁷ Белая, Ж.Е. Федеральные клинические рекомендации по диагностике, лечению и профилактике остеопороза / Ж.Е.Белая, К.Ю.Белова, Е.В.Бирюкова [и др.] // *Остеопороз и остеопатии*, – 2021. 24(2), – p.4-47;.

⁸ Shen Y, Huang X, Wu J, Lin X, Zhou X, Zhu Z, Pan X, Xu J, Qiao J, Zhang T, Ye L, Jiang H, Ren Y and Shan P-F (2022) The Global Burden of Osteoporosis, Low Bone Mass, and Its Related Fracture in 204 Countries and Territories, 1990-2019. *Front. Endocrinol.* 13:882241

⁹ Kelly, J.J. Bone turnover markers in osteoporosis // *Journal of the American Medical Association*, – 2019. Vol. 322, No. 23, – p.2344.

homocysteine (Hcy) in the study of bone metabolism during osteoporosis is more widely studied.

Cartilage glycoprotein-39 (HCgp39, YKL-40) is synthesized in chondrocytes, in activated macrophages of synovial cells, in neutrophils, and osteosarcoma cells - that is, in inflammatory cells¹⁰.

Osteoactivin (GPNMB) is a new-generation glycoprotein formed as a result of the differentiation of osteoblasts and plays a role in bone remodeling. Thus, it accelerates the differentiation of osteoclasts but slows down their functions¹¹.

Homocysteine (Hcy) is a sulfur-containing amino acid, which is formed from the metabolic cycle of methionine. According to research data, the risk of fracture is 2-4 times higher in patients with a high concentration of Hcy in the blood¹².

The role of biomarkers such as cartilage glycoprotein-39 (HCgp39, YKL-40), osteoactivin (GPNMB), and homocysteine (Hcy) in the pathogenesis of osteoporotic fractures is not fully defined and the research conducted in this field is sparse. The study of the role of protein and peptide regulators in the remodeling processes characteristic of osteoporosis may allow the development of new drugs for therapeutic purposes, as well as monitoring the dynamics of fracture recovery. It is necessary to conduct complex research in order to study the role of these indicators in the development of osteoporosis and clarify their practical importance during the healing period of fractures. The listed evidence determines the relevance of the research and justifies its goals and objectives.

The object and subject of the research. The object of the study is patients with osteoporosis, fractures in people without osteoporosis, and with osteoporotic fractures.

¹⁰ Komabashiri, N., F. Suehiro, M. Ishii [et al.] Efficacy of chitinase-3-like protein 1 as an in vivo bone formation predictable marker of maxillary/mandibular bone marrow stromal cells // *Regenerative Therapy*, - 2021.18(3), p.38-50.

¹¹ Abdelmagid, SM, Belcher JY, Moussa FM, [et al.] Mutation in osteoactivin decreases bone formation in vivo and osteoblast differentiation in vitro // *Am J Pathol.*, - 2014. 184(3), - p, 697-713.

¹² Kuroda, T. Tanaka, S. Saito, M. [et al.] Plasma level of homocysteine associated with severe vertebral fracture in postmenopausal women // *Calcif. Tissue Int.*, - 2013. vol. 93 (3), - p. 269–275.

The subject of the research is the more informative and sensitive protein and peptide regulators that we determined in the blood samples of these patients before and after treatment.

The goal and objectives of the research work. The purpose of the research was the study and clinical application of clinically significant, more sensitive, specific, and modern diagnostic biomarkers in metabolic processes occurring in bone and cartilage tissue during osteoporosis and osteoporotic fractures.

Tasks of the Research:

1. Comparative study of calcium-phosphorus exchange (calcium, phosphorus, magnesium, total protein) and indicators regulating this exchange (alkaline phosphatase and vitamin D) in patients with osteoporosis, osteoporotic fractures, and patients without osteoporosis but with fractures;

2. Determination of the concentration of cartilage glycoprotein-39 (YKL-40), which is a protein and peptide regulator, in patients with osteoporosis, osteoporotic fractures, and patients without osteoporosis but with fractures and monitoring its dynamics during treatment.

3. Determination of the concentration of osteoactivin which is a protein and peptide regulator in patients without osteoporosis, osteoporotic fractures, and patients without osteoporosis but with fractures, and monitoring its dynamics during treatment;

4. Determination of the homocysteine concentration in patients with osteoporosis, osteoporotic fractures, and patients without osteoporosis but with fractures and monitoring its dynamics during treatment

5. Determination of correlations between protein and peptide indicators during treatment in the studied groups, evaluation of their specificity and informativeness.

Research methods. The concentration of calcium, phosphorus, magnesium, vitamin D, YKL-40, homocysteine, and osteoactivin concentration, total protein, and alkaline phosphatase activity in blood serum were determined by the immunoenzyme analysis method.

During the statistical calculations, variance analysis (ANOVA test), correlation analysis (Spearman test), discriminant analysis (ROC-analysis) methods were applied. For this purpose, the SPSS-22.0 package program was used, and the results were summarized in tables and diagrams

The main provisions for defense are:

1. Changes in bone mineral metabolism during osteoporosis, including a decrease in the level of vitamin D involved in the regulation of this metabolism and the ALP activity, increase the risk of fractures.

2. An increase in the concentration of cartilage glycoprotein-39 (YKL-40), osteoactivin, and homocysteine in blood serum during osteoporotic fractures proves that these indicators play a major role in the mechanism of fracture formation.

3. The reduction of cartilage glycoprotein-39 (YKL-40) and homocysteine concentration in blood serum, and the increase of osteoactivin concentration, are important in the process of fracture recovery, and this process is slower in osteoporotic fractures than in fractures in non-osteoporotic individuals.

4. Homocysteine and osteoactivin are highly informative and specific indicators in the diagnosis and treatment of osteoporotic fractures.

The scientific novelty of the research: A complex and comparative study of specific biomarkers of various protein and peptide natures, including indicators of bone metabolism, reflecting the pathogenesis of osteoporosis, was performed. The role of protein and peptide regulators (YKL-40, homocysteine, and osteoactivin) in the pathogenesis of fractures accompanied by osteoporosis was evaluated, and their prognostic value and importance during the fracture healing period were determined. For the first time, it was found that YKL-40, homocysteine, and osteoactivin play an important role in the recovery of fractures in patients with osteoporosis.

The scientific and practical significance of the research. The obtained results can clarify the role of cartilage glycoprotein-39 (YKL-40), homocysteine, and osteoactivin in the pathogenesis of

osteoporotic fractures, determine the risk of fractures, conduct an early diagnosis of the disease, and organize adequate treatment. The study of these indicators during osteoporotic fractures may allow a more precise understanding of the biochemical-molecular mechanisms of bone metabolism disorders. The obtained results reveal the role of regulators such as YKL-40, homocysteine, and osteoactivin along with calcium-phosphorus exchange indicators of bone metabolism in the diagnosis of osteoporotic fractures.

Approbation and application. The materials of the dissertation were presented and discussed at the scientific conference dedicated to the 90th anniversary of the birth of a Correspondent member of ANAS, honored scientist, prof. D. Hajiyeu (Baku, 2019); XXIII Republican scientific conference of doctoral students and young researchers (Baku, 2019); XXIV Republican scientific conference of doctoral students and young researchers (Baku, 2021); the XVIII International Scientific Symposium "The Past and Future of the Turkic World" (Kazakhstan, 2021); the 8th International Medicine and Health Sciences Researches Congress (UTSAK), (Ankara, 2021); the International Scientific-Practical Conference on "Actual Problems of Medicine" dedicated to the "Year of Shusha" (Baku, 2022); 11th International conference: Achievements and challenges in biology devoted to 120th anniversary of professor M.Akhundov (Baku, 2022); the IV Congress of Azerbaijan Orthopedics and Traumatologists dedicated to the Second Karabakh War (Baku, 2022); the 2nd International Azerbaijan Congress of Hematology Specialists (Baku, 2022); the scientific-practical conference "Actual problems of biochemistry and medicine" dedicated to the 80th anniversary of prof. A.M. Efendiyev (Baku, 2023); scientific-practical conference "Actual problems of medicine" dedicated to the 100th anniversary of H.A. Aliyev (Baku, 2023); the 1st International Azerbaijan Laboratory Medicine Congress dedicated to the 100th anniversary of H.A. Aliyev (Baku, 2023), "WorldLab-EuroMedLab Roma 2023 Congress" (Roma, 2023), "VII international scientific conference" (Dortmund, Germany 2023).

23 scientific works were published on the subject of the dissertation - 9 articles, 3 of which were published abroad, 14 reports

and theses, 4 of them abroad, were discussed at republican and international conferences.

The results of the dissertation work are applied in the teaching process of the Biochemistry Department of the Azerbaijan Medical University.

Name of the organization where the dissertation is performed. The dissertation work was performed in the Clinical-diagnostic laboratory of the Scientific Research Institute of Traumatology and Orthopedics and the Scientific Research laboratory of the Department of Biochemistry of the Azerbaijan Medical University.

The structure of the dissertation with a sign including a separate volume of the structural units of the dissertation. The dissertation consists of 171 computer pages (254049 characters). Introduction – 9 pages (16046 characters), Chapter I – 26 pages (52767 characters), Chapter II – 12 pages (20566 characters), Chapter III –56 pages (94863 characters), Chapter IV – 34 pages (66992 characters), Conclusion – 2 pages (2312 characters), practical recommendations – 1 page (503 characters).

The dissertation is illustrated with 24 tables and 11 figures.

The list of literature refers to 225 sources (19 of them in Azerbaijani and 206 in foreign languages).

MATERIALS AND METHODS

To achieve the set goal, 111 patients aged 45-85 who applied to the Scientific Research Institute of Traumatology and Orthopedics of the Republic of Azerbaijan were selected. The average age of patients was 61.2 ± 0.8 (Me=60.0; Quartile 1=55.0; Quartile 2=66.0). The patients included in the study were divided into 3 groups: osteoporotic patients (30 patients), fractures in non-osteoporotic individuals (FNOI) (36 patients), and the group of patients with osteoporotic fractures (45 patients). 17 practically healthy people were included in the control group (Figure 1).

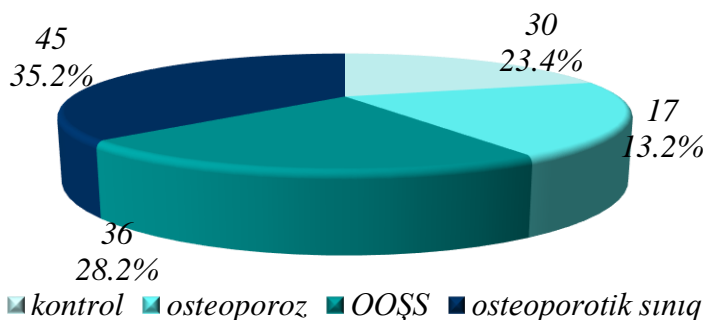


Figure 1. Research contingent

Patients included in the study were divided into 2 groups according to their ages: 45-60 years old and over 60 years old (Table 1).

Table 1.

Age and sex division of persons included in the study

			Groups					P _k
			Control	Osteoporosis	FNOI	Osteoporotic fracture	Total	
Sex	male	N	6	7	16	15	43	0.477
		N %	35.3%	23.3%	41.7%	33.3%	33.6%	
	female	N	11	23	20	30	85	
		N %	64.7%	76.7%	58.3%	66.7%	66.4%	
Age	45-60	N	7	15	23	18	63	0.166
		N %	41.2%	50.0%	63.9%	40.0%	49.2%	
	> 60	N	10	15	13	27	65	
		N %	58.8%	50.0%	36.1%	60.0%	50.8%	

Note: FNOI – fractures in non-osteoporotic individuals

Biochemical indicators were determined to confirm the diagnosis of osteoporosis in all patients whose blood samples were taken. However, a certain number of patients in each group were selected and protein and peptide indicators were determined in 3 stages: on the first day of admission to the hospital, on the 10th day of treatment, and 1 month after the start of treatment. Thus, 14 healthy

people were selected for the control group. 14 people were selected for the group of patients with osteoporosis, 15 people for the group of fractures in people without osteoporosis, and 25 people for the group of people with osteoporotic fractures. Thus, 162 blood samples were collected from 54 patients in 3 stages, and 14 blood samples were collected from healthy individuals, and a total of 176 serums were obtained. Human cartilage glycoprotein-39, osteoactivin, and homocysteine indicators were determined in each serum. Table 2 shows the proportions of these patients divided by age and sex into groups.

Table 2.

Division of patients and healthy individuals, whose protein and peptide indicators were determined, by age and sex

Research contingent		Number	Groups				Total	p _k
			Control	Osteoporosis	FNOI	Osteoporotic fracture		
Sex	male	n	5	2	8	7	22	0.293
		n %	35.7%	14.3%	53.3%	28.0%	32.3%	
	female	n	9	12	7	18	46	
		n %	64.3%	85.7%	46.7%	72.0%	67.7%	
Age, groups	45-60	n	7	5	10	8	30	0.663
		n %	50.0%	35.7%	66.7%	32.0%	44.1%	
	> 60	n	7	9	5	17	38	
		n %	50.0%	64.3%	33.3%	68.0%	55.9%	

RESEARCH METHODS

Patients who applied to the Admission Department of the Scientific Research Institute of Traumatology and Orthopedics of the Republic of Azerbaijan were placed for inpatient examination in the Traumatology Department after the first aid. They were diagnosed on the basis of X-ray, densitometry, ultrasound examination, and determination of biochemical indicators of bone metabolism. Of the 81 patients with fractures, 45 were patients with osteoporotic fractures.

Densitometry is an examination method that determines the mineral density of bone tissue. According to the size, thickness, and

density of the bones, the coefficients T (compared to the indicators of a healthy young organism of the same sex) and Z (compared to the organism of the same sex, weight, and age) are determined.

After the operation, the patients continued to be treated in inpatient care under the supervision of a doctor for 1 week and then were sent to outpatient treatment at home. During outpatient treatment, calcium (Ca), and vitamin D preparations were prescribed to the patients to speed up the bone regeneration process.

Pain, limitation of movement, and deformations of the spine were observed in patients with osteoporosis. Some patients with osteoporosis reported receiving prophylactic treatment for a long time, taking Ca and Vitamin D. After collecting detailed anamnesis, blood samples were collected from patients on an empty stomach. Blood samples were taken from all patients indicators were determined on the 10th day of the treatment and after 1 month.

In order to diagnose osteoporosis in the patients included in the study, calcium-phosphorus exchange and indicators regulating this exchange were analyzed along with bone densitometry indicators. These indicators playing an important role in the metabolism of the bone tissue are considered important factors in the development of osteoporosis.

The concentration of calcium, phosphorus, magnesium, and the activity of alkaline phosphatase in the blood of practically healthy and osteoporotic patients involved in the study were determined by biochemical methods.

The concentration of calcium (Ca), phosphorus (P), magnesium (Mg), total protein (TP), and activity of alkaline phosphatase (ALP) in blood serum were determined using the "Human" (Germany) reagent kit.

The concentrations of specific protein and peptide biomarkers (cartilage glycoprotein-39 (YKL-40, CH3L1), homocysteine (Hcy), osteoactivin (OA), vitamin D, which is the main regulator of calcium-phosphorus metabolism) in the blood serum of healthy individuals and patients included in the control group were determined by the method of enzyme immunoassay analysis (EIA) in the "Mindray MR-96A" immunoenzyme analyzer.

The concentration of YKL-40 was determined using the BOSTER (PicoKine™ ELISA) reagent kit. The concentration of osteoactivin in the blood serum of the individuals included in the research groups was determined by the "sandwich" method in the immunoenzyme analyzer using the BOSTER (PicoKine™ ELISA) reagent kit.

The concentration of homocysteine (Hcy) in the blood was determined by the "sandwich" method at a wavelength of 450 nm in an immunoenzyme analyzer using a reagent kit manufactured by the company "Cloud Clone" (Germany).

The concentration of vitamin D was analyzed based on the concentration of calcidiol (25(OH)D) in the blood serum using the reagent kit of the company "Bioactiva Diagnostica" (Germany).

All values obtained for indicators during the research were statistically analyzed taking into account modern recommendations. Qualitative analysis of the change of indicators was checked using the χ -Pearson Chi-Square criterion (ANOVA test), statistical integrity was determined by the Wilcoxon test (p_w), and correlation between indicators was checked using the Spearman test (ρ). The specificity and sensitivity of the indicators were determined on the basis of ROC curves (receiver operating characteristic).

All calculations were made in the EXCEL-2010 spreadsheet and SPSS-22.0 package program, the results were summarized in tables and figures.

Status of calcium-phosphorus exchange and parameters regulating this exchange in patients with osteoporosis

The role of microelements in the development and formation of the bone skeleton is related to their catalytic function in the synthesis of organic substances of the bone matrix. Being important for the normal growth and development of the skeleton, microelements play the role of metalloenzymes in the synthesis of collagen and proteins that form the structure of bones. The role of calcium, phosphorus, and magnesium among micronutrients in bone metabolism has been studied more.

According to the results obtained during the determination of calcium-phosphorus metabolism indicators in patients with

osteoporosis, the value of the indicators in this group changed significantly compared to the control group. The concentration of calcium in these patients decreased by 37.7% ($p_U < 0.001$) compared to the control group, and the average value was 1.75 ± 0.07 mmol/l ($Me = 1.80$ mmol/l). A decrease in calcium concentration was observed in patients over 60 years old ($p_U = 0.770$).

Status of protein and peptide regulators of bone and cartilage metabolism in patients with osteoporosis

In recent years, scientific evidence has been obtained about the role of the inflammatory process in the development and progression of osteoporosis. Inflammatory mechanisms involved in the pathogenesis of osteoporosis have increased interest in biomarkers as new risk factors for this disease. One of them is human cartilage glycoprotein-39 or YKL-40.

Table 3 shows the results obtained during the study of protein and peptide regulators of bone and cartilage metabolism in patients with osteoporosis.

Table 3.

Protein and peptide regulators of bone and cartilage metabolism in patients with osteoporosis

Indicators	Groups	N	M	$\pm m$	95% interval		Min.	Max.	P_U
					LL	UL			
YKL-40	control	14	1601.7	200.4	1168.7	2034.7	354.9	2915.0	0.003
	osteoporosis	14	793.8	104.2	568.7	1018.9	261.2	1601.0	
Hcy	control	14	642.7	166.9	282.2	1003.2	10.6	2513.3	0.108
	osteoporosis	14	1758.4	556.0	557.2	2959.7	251.1	6305.2	
Osteoactivin	control	14	323.4	66.8	179.0	467.8	84.9	836.3	0.039
	osteoporosis	14	537.6	80.9	362.8	712.3	125.3	951.6	

Note: P_U - compared to the control group

In patients with osteoporosis, the concentration of YKL-40 decreased statistically significantly compared to the control group, and this decrease was 2.0 times ($p_U = 0.003$). During the study of Hcy and osteoactivin in this group, a statistically significant increase of 2.7 times ($p_U = 0.108$) and 66.2% ($p_U = 0.039$) was observed, respectively, compared to the control group.

Calcium-phosphorus metabolism during fractures in non-osteoporotic individuals and the status of parameters regulating this metabolism

The results of the study of calcium-phosphorus exchange during fractures in people without osteoporosis showed that the concentration of calcium in the blood was statistically significantly reduced by 36.9% ($p_U < 0.001$) compared to the control group and amounted to 1.76 ± 0.06 mmol/l ($Me = 1.90$ mmol/l) on average. This indicator did not change significantly ($p_U = 1,000$) compared to patients with osteoporosis. Calcium concentration tends to decrease in the age group over 60 compared to other age groups ($p_U = 0.528$).

Status of protein and peptide regulators of bone and cartilage metabolism in fractures of non-osteoporotic individuals

In patients without osteoporosis, the concentration of YKL-40 increased by 13.8% ($p_U = 0.458$) during fractures compared to the control group, and by 2.3 times ($p_U = 0.005$) compared to patients with osteoporosis. The Hcy concentration in these patients was found to increase significantly, by 5.6 times ($p_U < 0.001$) compared to the control group, and by 2.0 times ($p_U = 0.005$) compared to the patients with osteoporosis. The concentration of osteoactivin increased by 54.1% ($p_U = 0.067$) compared to the control group (Table 4).

Table 4.

Protein and peptide regulators of bone and cartilage metabolism during fractures in non-osteoporotic individuals

Indicators	Groups	N	M	$\pm m$	95% interval		Min.	Max.	P _U
					LL	UL			
YKL-40	Control	14	1601.7	200.4	1168.7	2034.7	354.9	2915.0	$p = 0,458$ $p_1 = 0,005$
	FNOI	15	1822.6	259.9	1265.2	2380.1	235.5	3599.2	
Hcy	control	14	642.7	166.9	282.2	1003.2	10.6	2513.3	$p < 0,001$ $p_1 = 0,005$
	FNOI	15	3570.0	619.6	2241.1	4898.8	1195.3	7984.5	
Osteoactivin	control	14	323.4	66.8	179.0	467.8	84.9	836.3	$p = 0,067$ $p_1 = 0,678$
	FNOI	15	498.5	87.1	311.8	685.3	135.2	1409.5	

Note: p – compared to the control; p_1 – compared to the patients with osteoporosis; FNOI – fractures in non-osteoporosis individuals

Bone metabolism indicators in osteoporotic fractures

Calcium-phosphorus exchange in osteoporotic fractures and the status of parameters regulating this exchange

In patients with osteoporotic fractures, the calcium concentration decreased by 40.1% ($p_U < 0.001$), magnesium 2.0 times ($p_U < 0.001$), vitamin D 5.3 times ($p_U < 0.001$) compared to the control group, and the activity of ALP decreased statistically significantly by 70.8% ($p_U < 0.001$). Although the concentration of phosphorus in this group decreased by 17.2% ($p_U = 0.152$) compared to the control group, this result was not statistically significant. The concentration of total protein in this group tended to decrease by 6.3% ($p_U = 0.294$) compared to the control group. As a result of disturbances in calcium, phosphorus, and vitamin D exchange, mineralization of the bone matrix leads to the development of osteoporosis.

Magnesium forms an association with calcium and phosphorus in bones. Magnesium decline can impair calcium absorption, transport, and utilization, leading to hypocalcemia. A decrease in the concentration of magnesium in the serum results in a violation of the conversion of vitamin D to its active form, stimulation of calcitonin, and weakening of the synthesis of PTH. As a result, the process of bone formation weakens, and resorption accelerates, causing loss of bone mass.

The obtained results indicate the necessity of using vitamin D preparations in the complex treatment of osteoporotic fractures (Figure 2).

Thus, the obtained results show that during osteoporotic fractures more serious disturbances in calcium-phosphorus exchange were detected than in fractures of non-osteoporotic individuals. Compared to fractures in non-osteoporotic individuals, the greater decrease in the concentration of magnesium and vitamin D, the activity of the ALP enzyme suggests a disturbance in the regulation of calcium-phosphorus metabolism in the pathogenesis of osteoporotic fractures¹³.

¹³ Həsənova, N.A. Osteoporoz zamanı sümük metabolizmi markerlərinin xüsusiyyətləri // Azərbaycan təbabətinin müasir nailiyyətləri jurnalı, – 2021, №4, – s 27-31

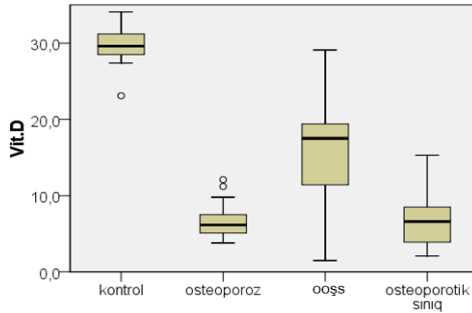


Figure 2. Changes in the concentration of Vitamin D in the examined patients

Status of protein and peptide regulators of bone and cartilage metabolism in osteoporotic fractures

The results obtained during the study of the concentration of protein and peptide regulators of bone and cartilage metabolism in the patient group with osteoporotic fractures are shown in Table 5.

Table 5.

Protein and peptide regulators of bone and cartilage metabolism in osteoporotic fractures

Indicators	Groups	N	M	±m	95% interval		Min.	Max.	P _U
					LL	UL			
YKL-40	Control	14	1601.7	200.4	1168.7	2034.7	354.9	2915.0	p=0.135
	osteoporotic fractures	25	2086.6	182.5	1709.9	2463.2	847.6	3490.5	p ₁ <0.001 p ₂ =0.567
Hcy	Control	14	642.7	166.9	282.2	1003.2	10.6	2513.3	p<0.001
	osteoporotic fractures	25	4204.2	501.5	3169.2	5239.2	395.9	7892.9	p ₁ =0.005 p ₂ =0.335
Osteoactivin	Control	14	323.4	66.8	179.0	467.8	84.9	836.3	p=0.015
	osteoporotic fractures	25	582.8	71.9	434.5	731.2	109.0	1581.5	p ₁ =0.861 p ₂ =0.349

Note: compared to p –control, p₁ –osteoporosis; p₂ –non-osteoporotic fractures

The obtained results show that compared to the control group, the concentration of YKL-40 in osteoporotic fractures increased by 30.3% (p_U=0.135); Hcy – 6.5 times (p_U<0.001); osteoactivin-by 80.2% (p_U=0.015). As seen, compared to patients with osteoporosis,

the concentration of YKL-40 increased 2.6 times ($p_U < 0.001$); Hcy - 2.4 times ($p_U = 0.005$). The increase in the concentration of YKL-40 in fractures of osteoporotic and non-osteoporotic individuals compared to patients with osteoporosis proves that this indicator increases mainly during fractures and plays a certain role in their recovery.

Thus, YKL-40 is a growth factor of connective tissue and is considered a strong migration factor of endothelial cells. YKL-40 also plays an important role in inflammatory processes and tissue remodeling, reflecting the progress of fracture healing. This is related to the mechanical pressure of the environment on the fracture recovery process and blood supply to the fractured area.

In recent years, a relationship between high homocysteine concentrations and the development of senile osteoporosis has been established. An increase in the concentration of homocysteine was found to increase the risk of fractures by 2-4 times compared to other people. This risk is independent of bone mineral density and other risk factors. Hyperhomocystinuria was found to increase the risk of osteoporotic fractures regardless of bone mass. It suggests that increased bone fragility due to high concentrations of Hcy is one of the main causes of quality changes in bones. Thus, Hcy directly damages osteoblasts in bone tissue and bone marrow stromal cells. An increase in the concentration of Hcy results in a decrease in the activity of osteoblasts. Hcy induces apoptosis of osteoblasts by accelerating oxidative stress. Besides, Hcy reduces the expression of lxyloxidase, which creates cross-links between collagen fibrils and causes the accumulation of extracellular pentoside in osteoblasts.

This evidence shows that Hcy impairs the viability and functions of osteoblasts, inhibits the formation of enzymatic cross-collagen bonds, and increases extracellular non-enzymatic pentoside bonds, thereby impairing the stiffness of bone tissue.

It has also been shown that Hcy accumulates on the surface of bones and reduces the density of trabecular or spongy bones, thereby affecting the biomechanical properties of bones. The research has revealed that 65% of Hcy binds to the collagen matrix and reduces bone strength.

Osteoactivin is synthesized in both osteoblasts and osteoclasts. Although the role of osteoactivin in the differentiation and functional activity of osteoblasts has been studied both in vivo and in vitro, its signaling mechanism in this process is not fully known.

For example, in a study using recombinant osteoactivin, it was found that osteoactivin stimulated the differentiation of osteoblasts through the CD44 mechanism. Osteoactivin stimulates the mineralization of the bone matrix. In addition, the acceleration of the synthesis of osteoactivin during fractures proves that it plays an important role in the pathogenesis of fractures and stipulates the practical application of these indicators in the early and differential diagnosis of osteoporotic fractures.

Thus, during osteoporotic fractures, the concentration of YKL-40, Hcy, and osteoactivin, which are protein and peptide regulators of bone and cartilage metabolism, significantly increased. The concentration of YKL-40 mainly increased in patients aged 45-60 years, while the concentration of Hcy and osteoactivin increased mostly in patients over 60 years of age.

An increase in this indicator is observed both in fractures of non-osteoporotic individuals and osteoporotic fractures. An increase in the concentration of Hcy during osteoporotic fractures indicates a high risk of fractures in these patients.

Status of protein and peptide regulators of bone and cartilage metabolism after treatment

Status of protein and peptide regulators of bone and cartilage metabolism after treatment in osteoporotic patients without fractures

Unfortunately, in daily clinical practice, even after osteoporotic fractures, there are many cases when the patient does not receive the necessary therapy. This causes the progression of the pathological process, failure of adhesion in the damaged bone, and the risk of repeated fractures. However, choosing the right treatment for osteoporosis during menopause helps to improve bone changes, reduce bone pain, and increase mobility. Therefore, all women with a confirmed diagnosis should receive therapeutic treatment before

complications develop. Such tactics are aimed at the prevention of disability and support of social and economic independence of elderly patients.

As we mentioned above, the concentrations of YKL-40, Hcy, and osteoactivin, which are protein and peptide regulators of bone and cartilage metabolism, were determined after 10 days and 1 month during the treatment period in the examined patients. The change in these indicators during the treatment period is presented in Figure 3. Although, after 10 days of the treatment of patients with osteoporosis, the concentration of YKL-40 increased by 12.6% ($p_w=0.158$) compared to pre-treatment results, the value of this indicator was 61% lower ($p_U=0.022$) compared to the control group. After 1 month, the concentration of YKL-40 did not change significantly compared to the results obtained after 10 days ($p_w=0.124$). The concentration of Hcy increased by 15.0%. According to comparative calculations, the concentration of Hcy remained 3.0 times higher ($p_U=0.141$) than in the control group after treatment, but it was 54.4% ($p_U=0.015$) lower compared to the FNOI group and 43.2% ($p_U=0.128$) lower than in osteoporotic fractures. After 1 month of treatment, the concentration of Hcy increased by 15.0% compared to the results obtained before treatment ($p_w=0.510$), but it changed very little compared to the results after 10 days of treatment ($p_w=0.158$).

Although the concentration of osteoactivin after 10 days of the treatment increased statistically significantly by 50.0% compared to the pre-treatment results, this increase was 2.5 times ($p_U=0.024$) higher than in the control group. This result is not significantly different from that of the FNOI group ($p_U=0.256$), and compared to patients with osteoporotic fractures, it increased by 32.0% ($p_U=0.558$). After 1 month of treatment, the concentration of osteoactivin in patients with osteoporosis increased by 47.8% compared to the results obtained before treatment ($p_w=0.026$).

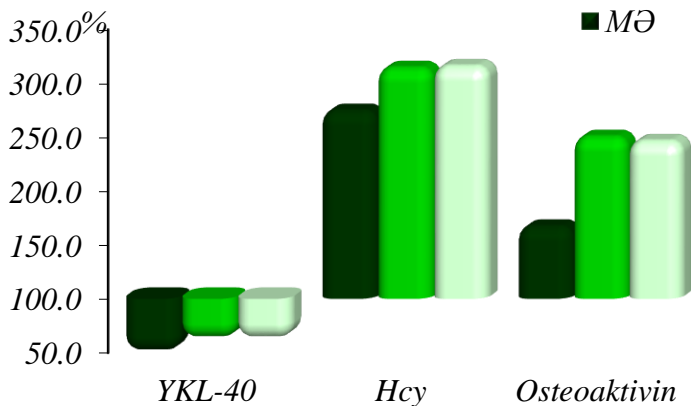


Figure 3. Changes in protein and peptide regulators of bone and cartilage metabolism during treatment of patients with osteoporosis without fractures

Thus, after the treatment, the concentration of YKL-40, Hcy, and osteoactivin decreased in patients with osteoporosis.

The obtained results prove that the decrease in the concentration of YKL-40 during osteoporosis increases the risk of fractures.

Status of protein and peptide regulators of bone and cartilage metabolism after fracture treatment in non-osteoporotic individuals

The concentrations of YKL-40, Hcy, and osteoactivin, which are protein and peptide regulators of bone and cartilage metabolism, were determined after 10 days and 1 month of treatment in non-osteoporotic individuals. The results are shown in Figure 4.

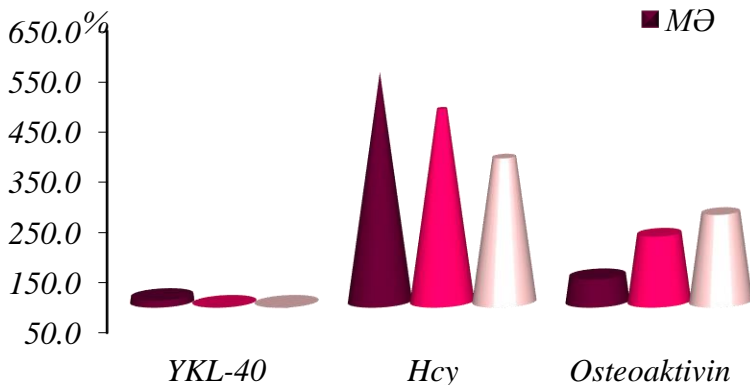


Figure 4. Changes in protein and peptide regulators of bone and cartilage metabolism during treatment of fractures in non-osteoporotic individuals

After 10 days of treatment of fracture in non-osteoporotic individuals, the concentration of YKL-40 was statistically significantly reduced by 15.3% compared to pre-treatment results ($p_w=0.001$). After 1 month, the concentration of YKL-40 significantly decreased by 30.0% compared to pre-treatment results ($p_w=0.001$). Although the concentration of Hcy decreased by 15.0% after 10 days, it remained 4.8 times ($p_u<0.001$) higher than that of the control group. 1 month after treatment, a 43.0% decrease in Hcy concentration was observed compared to pre-treatment results ($p_w=0.003$). The concentration of osteoactivin after 10 days of treatment increased by 53.8% compared to the indicators before treatment in all patients (15 patients – 100%). As seen from the results, the concentration of osteoactivin remained statistically significantly higher (2.4 times) than that of the control group ($p_u=0.001$). After 1 month, a statistically significant increase of 2 times compared to the results before treatment was observed in all patients (15 patients – 100%) ($p_w=0.001$).

Status of protein and peptide regulators of bone and cartilage metabolism after treatment of osteoporotic fractures

The concentration of YKL-40 in osteoporotic fractures did not change significantly after 10 days of treatment compared to the pre-treatment results ($p_w=0.563$). This indicator remained 29.0% ($p_u=0.057$) higher than that in the control group. After 1 month, the concentration of YKL-40 was found to be slightly decreased compared to the pre-treatment results ($p_w=0.353$). The Hcy concentration significantly decreased (by 46.0%) compared to pre-treatment values after 10 days ($p_w<0.001$). Comparative calculations show that the concentration of Hcy remained statistically significantly higher (by 4.5 times) compared to the control group ($p_u<0.001$). A 96.0% decrease in the concentration of Hcy compared to pre-treatment values was observed 1 month after treatment ($p_w<0.001$). The concentration of osteoactivin changed very little after treatment ($p_w=0.716$). This indicator remained 89.5% ($p_u=0.003$) higher than that for the control group.

The evaluation of the concentration of osteoactivin after 1 month of treatment showed that the concentration of osteoactivin tended to increase compared to the indicators before treatment ($p_w=0.840$) (Figure 5).

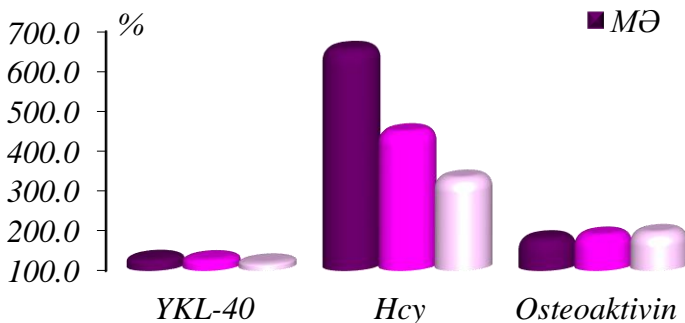


Figure 5. Changes in protein and peptide regulators of bone and cartilage metabolism during treatment of osteoporotic fractures

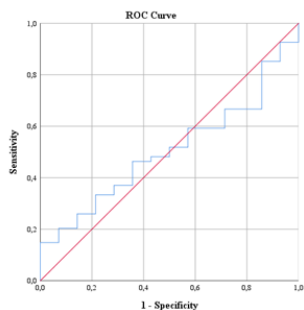
Thus, after the treatment of osteoporotic fractures, the concentration of YKL-40 and osteoactivin did not change significantly, but a statistically significant decrease in the

concentration of Hcy was observed. This shows that the healing process of osteoporotic fractures is slow compared to FNOI. The treatment prevents the aggravation of osteoporosis¹⁴.

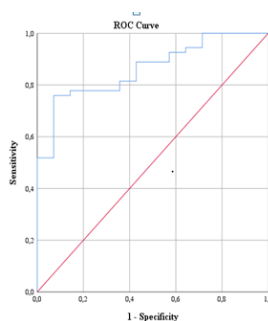
Determination of specificity and sensitivity of protein and peptide regulators of bone and cartilage metabolism, the study of correlations between indicators

The ROC (Receiver Operating Characteristic) statistical analysis method was used to determine the specificity and sensitivity of the studied protein and peptide regulators of bone and cartilage metabolism.

Based on the ROC analysis, it was found that the specificity area of YKL-40 was 0.505 ± 0.077 , the limits changed between 0.354-0.656 at 95% CI were, $p=0.952$. The specificity area determined on the basis of the ROC curve of Hcy was 0.862 ± 0.047 , and at 95% CI, limits are observed to vary from 0.770 to 0.954, $p<0.001$. The area of osteoactivin determined by the ROC curve was shown as 0.725 ± 0.083 , and at 95% CI, the lower limit was 0.561 and the upper limit was 0.888, $p=0.010$ (Figure 6).

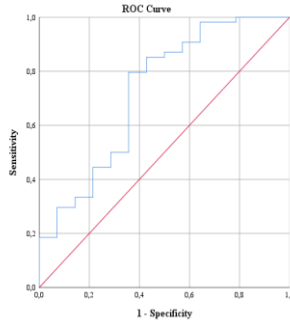


Human cartilage glycoprotein -39



Homocysteine

¹⁴ Гасанова, Н.А. Роль человеческого хрящевого гликопротеина, гомоцистеина и остеоактивина в костно-хрящевом метаболизме в восстановительном периоде остеопоротических переломов // Клиническая лабораторная диагностика, – 2023. №1, – с.12-17. doi:10.51620/0869-2084-2023-68-1-12-17.



Osteoactivin

Figure 6. ROC analysis of protein and peptide regulators of bone and cartilage metabolism in the blood serum of the examined patients

Variation of test results	Area	Standard error	P reliability	95% confidence interval	
				Lower limit	Upper limit
Human cartilage glycoprotein -39	0.505	0.077	0.952	0.354	0.656
Homocysteine	0.862	0.047	0.000	0.770	0.954
Osteoactivin	0.725	0.083	0.010	0.561	0.888

A positive correlation was observed between Vitamin D ($\rho=0.577$, $p=0.003$), ALP ($\rho=0.428$, $p=0.033$), total protein ($\rho=0.548$, $p=0.005$) and osteoactivin ($\rho=0.490$, $p=0.013$); between vitamin D and total protein ($\rho=0.488$, $p=0.013$), a negative correlation between Hcy ($\rho=-0.441$, $p=0.027$) and Z-criterion, and a positive correlation with osteoactivin ($\rho=0.511$, $p=0.009$) were detected in patients with osteoporotic fractures.

It can be concluded that the deficiency of vitamin D and the decrease in the activity of ALP can lead to calcium deficiency. Vitamin D deficiency can also cause a decrease in total protein. A deficiency of calcium, in turn, can lead to a violation of the protein content of bones and a weakening of the synthesis of osteoactivin. An increase in Hcy in patients with osteoporosis can lead to a decrease in osteoactivity and an increase in the risk of bone fractures.

Thus, the above results show once again that osteoactivin plays an important role in the recovery of osteoporotic fractures.

In general, a positive correlation was detected between ALP and calcium ($\rho= 0.291, p=0.033$) and vitamin D ($\rho= 0.379, p=0.005$) in all studied groups. Thus, the weakening of the ALP activity and the lack of vitamin D lead to a negative calcium balance.

In these patients, a positive correlation was observed between T-criterion and magnesium ($\rho= 0.333, p=0.014$), vitamin D ($\rho= 0.503, p<0.001$) and ALP ($\rho= 0.326, p=0.016$); between Z-criterion and magnesium ($\rho= 0.355, p=0.008$), vitamin D ($\rho= 0.444, p=0.001$) and ALP ($\rho= 0.330, p=0.015$). The evidence obtained as a result of the correlation analysis once again shows that the decrease in the concentration of magnesium and vitamin D in the body, the weakening of the ALP activity are important factors in the occurrence of osteoporosis in bones. In other words, bone densitometry indicators decrease.

A positive correlation was found between Hcy, YKL-40 ($\rho= 0.321, p=0.018$), and osteoactivin ($\rho= 0.276, p=0.044$) (Figure 7).

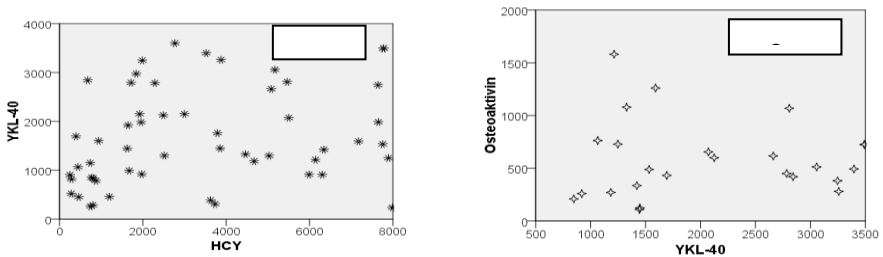


Figure 7. Correlation between Hcy, YKL-40, and osteoactivin in patients with osteoporotic fractures

Thus, the obtained results show that the disturbance of calcium-phosphorus exchange has a direct effect on the concentration of protein and peptide regulators of bone and cartilage metabolism. An imbalance in the metabolism of Hcy can lead to disruption of bone remodeling and osteoporosis. Regulation of Hcy overproduction may facilitate additional therapeutic approaches in the prevention of osteoporosis. A significant increase in the

concentration of YKL-40 and osteoactivin during fractures proves their important role in fracture healing. In contrast to fractures in non-osteoporotic individuals, in osteoporotic fractures, the lower increase in the concentrations of YKL-40 and osteoactivin explains the poor rate of fracture healing in these patients¹⁵¹⁶¹⁷.

CONCLUSIONS

1. In patients with osteoporotic fractures compared to patients with fractures without osteoporosis, statistically significant decrease by 2.3 times, 27.5% and 44.9% ($pU < 0.001$), respectively, in the concentrations of vitamin D, magnesium, and alkaline phosphatase indicates more serious changes in mineral metabolism of these patients [3,7,9,23]

2. A 2.0-fold decrease in the concentration of YKL-40 in the blood serum of osteoporotic patients compared to the control, but an increase by 13.9% and 30.3%, respectively in patients with osteoporotic fractures and fractures in non-osteoporotic individuals proves the role of this indicator in the pathogenesis of fractures. While the concentration of YKL-40 during treatment did not change significantly in patients with osteoporosis and osteoporotic fractures, a statistically significant decrease by 30.0% in fractures of non-osteoporotic individuals suggests that it is an important factor in the fracture healing process [5,8,14,17,19].

3. Increases in homocysteine concentration in patients with osteoporosis - 2.7 times, in persons without osteoporosis but with fractures - 5.6 times, and in patients with fractures of osteoporotic origin - 6.5 times compared to control prove a great role of this indicator in assessing the possibility of fracture risk. 1 month after

¹⁵ Həsənova, N.A. Osteoporoz və sınıqların bərpası dövründə qan serumunda insan qığırdaq qlikoproteini konsentrasiyasının dəyişmələri // – Bakı: Azərbaycan Tibb Jurnalı, – 2021. №4, – s 32-35.

¹⁶ Azizova, G. I., Hasanova, N.A., Dadashova, A.R. Dynamics of osteoactivin in patients with osteoporotic fractures // Bulletin of problems biology and medicine”, – 2022. Issue 1 (163), – p.119-122.

¹⁷ Hasanova, N.A. The dynamics of Homocystene level in the osteoporosis patients which accompanied by the fracture // Ukr. Biochem. J., – 2022. 94(3), – p.53-58.

the start of treatment, homocysteine concentration in people without osteoporosis but with fractures decreased by 43.0%, and in patients with osteoporotic fractures it decreased by 96.0%, which stipulates the importance of this indicator in monitoring the positive dynamics of fracture recovery [2,13,16,21,22].

4. The increase in the concentration of osteoactivin compared to the control in patients with osteoporosis, without osteoporosis but with fractures, and with osteoporotic fractures, respectively, by 66.2%, 54.1%, and 80.2% indicates the important role of this indicator in the pathogenesis of osteoporotic fractures. 1 month after starting treatment, an 81.6% increase in the concentration of osteoactivin in patients without osteoporosis but with fractures and a slight change in patients with osteoporotic fractures are explained by the late healing of these fractures [6,10,17,18].

5. A negative correlation was found between Hcy ($\rho = -0.441$, $p = 0.027$) and Z-criterion, and a positive correlation between YKL-40 ($\rho = 0.321$, $p = 0.018$) and osteoactivin ($\rho = 0.276$, $p = 0.044$) in the examined patients. Based on the sensitivity and specificity indicators, the ROC curve was constructed and it was found that homocysteine and osteoactivin are tests with high overall diagnostic value and informativeness in predicting fractures during osteoporosis and can be used during the treatment of fractures [4,11,12,15,20].

PRACTICAL RECOMMENDATIONS

1. For the early diagnosis of bone fractures in patients with osteoporosis, it is recommended to determine the concentration of protein and peptide-based regulators of bone and cartilage metabolism: YKL-40, homocysteine, and osteoactivin, along with bone densitometry criteria.

2. During the healing of osteoporotic fractures, the determination of the concentration of homocysteine and osteoactivin together with the regulation of calcium-phosphorus exchange can be used as tests with high informativeness, specificity, and sensitivity during the treatment period.

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Abbreviations and conventional signs

LL	– Lower limit on the 95% interval
ALP	– alkaline phosphatase
CT	– calcitonin
Hcy	– homocysteine
YKL-40	– cartilage glycoprotein
PTH	– parathormone
DM	– diabetes mellitus
BMD	– bone mineral density
MSCs	– mesenchymal stem cells
Me	– median
SE	– standard error
M	– mean value
max	– maximum
min	– minimum
MRT	– Magnetic Resonance Tomography
ROC	– receiver operating characteristic (an integral indicator of sensitivity and specificity of the test)
US	– ultrasound
TDV	– total diagnostic value
WHO	– World Health Organization
UL	– Upper limit on the 95% interval
σ	– mean squared error

The defense will be held on __01 december__ _2023 at 14:00 at the meeting of the Dissertation Council FD 2.07 of Supreme Attestation Commission under the President of the Republic of Azerbaijan operating at Azerbaijan Medical University

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Abstract was sent to the required addresses on ____ _2023.

Signed for print: 20.10.2023

Paper format: 60x84 1/16

Volume: 37 934 characters

Number of hard copies: 20