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Experimental Medicine

Biochemical Markers of Bone and Cartilage Tissues' Metabolism in Patients with the 4th Stage Knee Osteoarthritis

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The higher the extend of the joint cartilage destruction, the more expressed are changes of the biochemical markers. The objective of this work is to study blood biochemical values in two age-related groups of patients suffering from the 4th stage of knee osteoarthritis. The sampling of the study included 23 women with bilateral 4th-stage osteoarthritis, divided into two age-related groups: (1st group: 64.44±1.02 years old; 2nd group: 75±1.63 years old). In their blood serum, we identified the concentration of calcium, phosphorus, alkaline phosphatase activity, osteocalcin levels, parathyroid hormone, and IIN-type propeptides procollagen. A significant rise in the concentration of osteocalcin in both groups, especially in the 2nd one (36.44% higher compared to the 1st group, P<0.05) was discovered. The concentration of parathyroid hormone was 37.67% (P<0.05) lower in the 2nd group, compared with the 1st one. Other values did not show any significant difference between the groups. Rise in the concentration of osteocalcin and drop in the concentration of parathyroid hormone at the 4th stage of knee osteoarthritis reflects metabolic disorders, especially expressed in the age-related group 75±1.63 years old. These biochemical values may be used to characterize the articular cartilage conditions at the late stage of the disease. *© 2025 Bull. Georg. Natl. Acad. Sci.*

osteoarthritis, biochemical markers, osteocalcin, parathyroid hormone, calcium, phosphorus, alkaline phosphatase, IIN type propeptidis procollagen, bone tissue metabolism

Osteoarthritis (OA) is a degenerative disease of joints, typical of progressive destruction of joint cartilage and concomitant changes in the adjacent tissues, leading to the occurrence of pain syndrome, oedema, and restriction in the motions of the joints, affecting significantly the patient's functional capacities [1]. OA of the knee (KOA) is a prevailing form of the degenerative-dystrophic disorder of a musculoskeletal system, specific to its chronic progression and expressed pain syndrome [2]. According to the results of many epidemiological studies, KOA is recognized to be the leading cause

of disability, associated with the pathologies of lower limbs, surpassing other specific forms by occurrence and the severity of consequences. This disease creates a significant social and economic burden, affecting significantly the patients' quality of life and the performance of the healthcare system in general [3].

Ethiogenesis and pathogenesis of KOA are multifactor ones and include the interaction of internal and external factors. Internal factors include gender peculiarities, age, and genetic liability to the disease, while external ones cover excessive mechanical loading, trauma injuries, and metabolic disorders. Epidemiological researches demonstrate that women are more prone to osteoarthritis, compared to men. Age remains the most significant risk factor for OA development, confirmed by the increase in the occurrence of the disease in older age-related groups. According to modern statistical data, about 240 million people worldwide suffer from symptomatic OA. At that, its incidence among 60-year-old people and above is 10% in men and 18% in women [4].

KOA is typical of significant changes in biochemical values that reflect destructive processes in cartilage tissues [5]. Initial pathological changes occur in cartilage tissue, where directly the degenerative processes take place. In bone tissue, the remodelling process disturbance leads to the development of subchondral sclerosis, formation of osteophytes and extension of the bone's epiphyseal portion. Synovial cover is also subjected to pathological changes, tends to hypertrophy and inflammation process development. These complex structural-functional disorders in different components of a joint predetermine the progression of the disease and identify the KOA's clinical pattern. Morphological characteristics of knee tissues and the content of metabolites in the blood serum are connected directly. The higher is the extent of the joint cartilage destruction, the more expressed are changes of the biochemical markers.

Modern data demonstrate that heterogeneity of the KOA's pathogenesis is reflected in the variety of combinations of biochemical markers that correlate with the extent of articular structures' degradation [6, 7]. The identification of the most sensitive biochemical values, considering the age-related specificity of a patient and stages of KOA development is of critical essence to extend our understanding of mechanisms of the disease's progression and to optimize therapeutic approaches. Identification of these specific markers allows us not only to assess the extent of pathological disorders but also to forecast the further progression of the disease, a key factor for a personal approach to the treatment and monitoring of the efficiency of therapeutic interventions for the KOA.

Osteocalcin, also known as GLA-protein of a bone, is a non-collagenous protein, forming about 1% of bone tissue's organic matrix. This protein acts as a key biomarker to assess bone tissue remodelling processes. Osteocalcin reflects the metabolic activity of osteoblasts, can take up calcium, and plays a viable role in bone tissue mineralization [8]. The identification of the concentration of osteocalcin in the blood serum of women has diagnostic value for the assessment of osteoarthritis development and enables us to monitor the condition of bone tissue remodelling during menopausal and post-menopausal periods. Thus, this biomarker is an informative value to evaluate the metabolic conditions of the bone tissue and a potential predictor of the development of pathological changes in joints.

Alkaline phosphatase is a widely recognized biochemical marker for osteogenesis. Within the context of metabolic diseases of bone tissue, the general activity of alkaline phosphatase demonstrates a positive correlation with the intensity of the bone tissue formation processes. In the geriatric population, there is a trend to moderate rise in the activity of this enzyme; this can serve as an index of disorders in mineralization processes and functional activity of fibroblasts. Such dynamic of alkaline phosphatase activity in senior persons requires a detailed analysis within the context of the

assessment of metabolic conditions of the bone tissue and diagnostics of potential changes in the system of bones and joints [9].

Parathyroid hormone (PTH) plays a viable role in osteogenesis regulation. Complex physiological system, including PTH, calcitonin, vitamins D, A, and C, ensures homeostasis of calcium and phosphorus by the control of their absorption, deposition, and excretion. The increase in the concentration of PHT in the blood flow leads to the negative balance of these minerals in the bone tissue, worsening the balance between osteogenesis and osteolysis towards the last mentioned. Hypersecretion of the PTH is associated with the reduced level of osteocalcin in bone tissue, as in the blood serum. Instead, insufficient secretion of the PHT may indicate adynamic bone disease.

The assessment of the synthetic activity of the 2nd type of collagen is informative in characterizing the metabolism of cartilage tissue. The process of the synthesis of this type of collagen includes the formation of an intermediary form – procollagen with an amin-containing N-final group (PIINP). Proteolytic cleavage of the PIINP takes place in the process of collagen fibrillar structure formation, which cat is an indicator of the intensity of its synthesis. The concentration of the PIINP in the blood serum is considered a direct correlative value of the quantity of newly-formed collagen. It is interesting that PIINP demonstrates higher sensitivity to variations, compared to osteocalcin.

Articular cartilage calcification is one of the most typical pathological signs of OA. The processes of subchondral bone tissue remodelling at the late stages of OA may be accompanied by an increase in the concentration of calcium and phosphorus in the subchondral micro-environment [10]. This dynamics of mineral composition plays a viable role in the pathogenesis of the disease and can serve as an indicator of the pathologic process progression.

Within the context of the above mentioned, an up-to-date objective is to identify biochemical markers of bone and cartilage metabolism in biological liquids of the body. These markers can become an important diagnostic tool to evaluate the progression of KOA. Complex analysis of these biomarkers enables us not only to reveal the disease at its early stages, but also monitor the dynamics of the pathological process, and has a crucial importance in choosing an optimal therapeutic strategy and assessing its effectiveness.

The objective of the research was to study blood biochemical values in two age-related groups of patients, suffering from the 4th stage KOA.

Methods of Study

The research covers 23 women, who at previous stages have been diagnosed with the 4th stage of OA. The mean age of the patients from the 1st group was 64.44±1.02, while the mean age of the patients in the 2nd group was 75±1.63. The research took place after the approval by the ethic committee of the Institute of Traumatology and Orthopedics according to the Helsinki Declaration of 2000, the EU Directive 86/609 on human participation in biomedical studies. All patients signed the form of an informed consent for participation in the research.

At the admission to the clinic, we collected anamnesis and carried out clinical examination of KOA patients. The symptoms included: painful flexion and extension of a leg, pain in the lateral or medial surface of the joint while walking, which disappeared in rest, joint instability, and expressed lameness.

The assessment of the extent of osteoporosis took place according to X-ray classification by Kellgren J. H. and Lawrence J. S. The 4th stage of the disease is typical of well-expressed signs: almost absent articular gap, multiple osteophytes, and deformity of the joint.

Blood serum served as the material for the study. Using standard test systems Roche Diagnostics, we determined the concentration of calcium, phosphorus, and activity of alkaline phosphatase with Cobas-311 biochemical analyzer. By the

method of immune-reference analysis, we indicated the concentration of osteocalcin, parathyroid hormone, and type IIN propeptide procollagen, using Cobas 411 immune-reference analyzer and Roche Diagnostics test systems. For the statistical processing of the data, we used Origin Pro 8.5 software. For the study, we determined mean values (x) with a standard deviation (SD). The reliability of the difference between the groups has been assessed according to t Student criterion. At $P<0.05$, the changes were considered significant.

Results and Discussion

According to the collected data, mean values of calcium and phosphorus concentration in the blood serum of patients suffering from the 4th stage of bilateral KOA didn't change significantly, compared to clinically healthy people and between the groups (Table 1). The interrelation of the levels of calcium and phosphorus remained within 1.93 – 1.94 and had no significant difference from the same in healthy people. Our results correlate with the same of other authors [11] and witness that calcium-phosphorus homeostasis in blood changes insignificantly at destructive processes at the background of the 4th stage of KOA.

Table. Biochemical values of bone and cartilage metabolism in women of different ages with the 4th stage of the bilateral KOA

Values	Age (years old)	
	64.44±1.02 (1st group)	75±1.63 (2nd group)
Osteocalcin, ng/ml	25.41±2.61	34.67±2.53*
Parathyroid hormone, ng/ml	37.88±5.13	23.61±1.82*
Terminal type IIN propeptide procollagen, ng/ml	55.8±5.02	51.72±3.91
Alkaline phosphatase, O/l	66.36±5.43	53.01±4.21
Ca, mmol/l	2.02±0.08	1.90±0.06
P, mmol/l	1.04±0.04	0.99±0.06
Ca/P rate	1.94±0.1	1.93±0.08

*P <0.05 regards the 1st group values

At that, they measured the concentration of osteocalcin in the blood serum of the patients from both groups and discovered its trend to rise, compared to normal values. Thus, in patients of the 1st group, this value was 15.5% higher, and in the 2nd group – by 57.59% higher. It was also 36.4% higher in the blood serum of the 2nd group, compared to the 1st one ($P<0,05$, Table).

Osteocalcin is emitted into the blood in the process of bone tissue formation, as during the resorption thereof [12, 13]. One of the specific features of the KOA at its latest stage is the rise of osteocalcin in the background of the low mineralization of the extracellular matrix with osteoblasts. That's why, its rise, which we have discovered, may witness the increasing synthetic activity of osteoblasts. This fact is also approved by our data about the activity of the alkaline phosphatase in the blood serum: the 2nd group showed its decrease by 20.1% ($P>0.05$, Table). However, there may be functional insufficiency of osteoblasts, showing very slow proliferation and low mineralization capacity [14, 15].

The concentration of the type IIN propeptid procollagen in both groups had no significant difference, compared to clinically healthy people. However, we observed its trend to be decreased by 7.31% in the blood serum of the 2nd group patients, compared to those from the 1st one ($P>0.05$).

The concentration of the prothyroid hormone in the blood serum of the 2nd group, compared to the 1st one, was 37.67% lower ($P<0.05$). The reason may be the disturbance of the tempo of osteogenesis and osteolysis, with the prevalence of the last mentioned.

Our results, relating to the changes in osteocalcin and parathyroid hormone witness significant destructive changes in the organic matrix and cartilage tissue in patients with the 4th stage of the KOA.

Conclusion

Thus, according to the results of the biochemical study of the blood serum of patients from both age-related groups, suffering from the 4th stage of a bilateral KOA, concentrations of osteocalcin and parathyroid hormone were moderately changed. The rise in the concentration of osteocalcin and the drop in the same of parathyroid hormone at the 4th stage of KOA reflects metabolic changes, especially for the age-related group 75±1.63. These data demonstrate the possibility of using the values of the content of osteocalcin and parathyroid hormone for an extra diagnostics of articular cartilage conditions in osteoarthritis patients.

ექსპერიმენტული მედიცინა

ძვლისა და ხრტილოვანი ქსოვილების მეტაბოლიზმის ბიოქიმიური მარკერები მუხლის მეოთხე სტადიის ოსტეოართრიტის მქონე პაციენტებში

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(წარმოდგენილია აკადემიის წევრის რ. ხეცურიანის მიერ)

წინამდებარე ნაშრომის მიზანია სისხლის ბიოქიმიური მაჩვენებლების შესწავლა მუხლის მეოთხე სტადიის ოსტეოართრიტით დაავადებულ პაციენტთა 2 ასაკობრივ ჯგუფში. კვლევაში ჩართული იყო აღნიშნული დაავადების მქონე 23 ქალი, გაყოფილი 2 ასაკობრივ ჯგუფად (პირველში შედიოდა 64,44±1,02 ასაკის, ხოლო მეორეში 75±1,63 წლოვანების ქალბატონები). მათ სისხლის შრატში აღმოჩნდა კალციუმის კონცენტრაცია, ფოსფორი, ტუტე ფოსფატაზას აქტივობა, ოსტეოკალცინის დონეები, პარათირეოიდული ჰორმონი და IIN ტიპის პროპეპტიდების პროკოლაგენი. ჩვენ აღმოვაჩინეთ ოსტეოკალცინის კონცენტრაციის მნიშვნელოვანი მატება ორივე ჯგუფში, განსაკუთრებით მეორე ჯგუფში (36,44%-ით მეტი პირველ ჯგუფთან შედარებით, P<0,05), რომელშიც პარათირეოიდული ჰორმონის კონცენტრაცია იყო 37,67%-ით (P<0,05) ნაკლები პირველ ჯგუფთან შედარებით. სხვა მაჩვენებლებმა არ აჩვენა რაიმე მნიშვნელოვანი განსხვავება ჯგუფებს შორის. მუხლის ოსტეოართრიტის მეოთხე სტადიაზე ოსტეოკალცინის კონცენტრაციის მატება და პარათირეოიდული ჰორმონის კონცენტრაციის დაქვეი-

თება ასახავს მეტაბოლურ დარღვევებს, რაც განსაკუთრებით გამოხატულია 75±1,63 ასაკის ჯგუფში. ეს ბიოქიმიური მაჩვენებლები შეიძლება გამოყენებულ იქნეს სასახსრე ხრტილის მდგომარეობის დასახასიათებლად დაავადების გვიან ეტაპზე.

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