

INDICATORS OF THE OXIDANT-ANTIOXIDANT SYSTEM IN THE SYNOVIAL FLUID OF PATIENTS WITH OSTEOARTHRITIS AFTER SARS-CoV2 INFECTION

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The article examines the state of the oxidant-antioxidant balance in the synovial fluid of patients with osteoarthritis after the 2019 coronavirus disease (COVID-19). In people with chronic diseases, COVID-19 can lead to a more severe course and development of complications. The aim of the work was to determine a number of indicators of the oxidant-antioxidant balance in the synovial fluid of patients with osteoarthritis after SARS-CoV2 infection. Among such patients there is a special group with osteoarthritis are a special group. Two groups of patients took part in the research: patients with osteoarthritis of the knee joints of the II-III degree and patients with osteoarthritis of the knee joints of the II-III degree, who suffered mild to moderate form of COVID-19 6-9 months ago. In the synovial fluid of patients from all experimental groups were evaluated the concentration of superoxide radical, hydrogen peroxide and enzymatic activity of superoxide dismutase and catalase according to standard biochemical methods. It was established, that in synovial fluid of patients with osteoarthritis of knee joints who have had COVID-19, increase the concentration of reactive oxygen (superoxide radical and hydrogen peroxide) and decrease the activity of antioxidant enzymes (superoxide dismutase and catalase). The obtained results indicate a deviation of the oxidative-antioxidant balance and the development of oxidative stress directly in the joint. So, the intensification of free radical processes in the joint of patients with osteoarthritis after infection with COVID-19 can cause a more severe course of osteoarthritis.

Key words: SARS-CoV-2, osteoarthritis, synovial fluid, free radical processes, antioxidant system.

Connection of the publication with planned research works.

Biochemical studies were carried out at the Department of Biochemistry of the Educational and Scientific Center «Institute of Biology and Medicine» of Taras Shevchenko National University of Kyiv within the framework of the research topic «Pathologies of joints caused by metabolic disorders in the post-Covid period» (state registration number: 0122U001909).

Introduction.

The 21st century pandemic disease affecting the human population is the 2019 coronavirus disease (Coronavirus disease 2019, COVID-19), which is caused by the severe acute respiratory syndrome virus 2 (SARS-CoV-2) [1]. According to data from the World Health Organization (WHO) (<https://covid19.who.int/>), as of December 1, 2022, there were 639,572,819 confirmed cases of COVID-19 worldwide, including 6,615 258 deaths.

Coronaviruses can cause the development of a respiratory disease, which can range from a mild disease (similar to a cold) to a severe condition - viral pneumonia [2, 3]. Patients with COVID-19 present with a variety of clinical manifestations and symptoms, including fatigue, fever, cough, loss of smell or taste, and headache. Among patients, about 30% also report the presence of disturbances in the functioning of the gastrointestinal tract (diarrhea, nausea, abdominal pain) [4]. The most frequent complications in patients with COVID-19 are pneumonia, disorders of the cardiovascular system, kidney failure, arthralgias and other pathologies [5-7]. Often, the development of complications is observed in patients with COVID-19 who were elderly or had other underlying diseases, such as obesity, hypertension, diabetes, diseases of the heart, lungs, musculoskeletal system, and others.

Thus, in people with chronic pathologies, COVID-19 can aggravate the course of the underlying disease [8, 9].

Among such patients with chronic diseases, patients with pathologies of the musculoskeletal system, particularly osteoarthritis, are an important group. Osteoarthritis is a chronic degenerative disease of the joints, which is characterized by the loss of cartilage tissue in the joints, the formation of a foci of inflammation, and is the main reason for the development of disability and incapacity of people. SARS-CoV-2 viral infection poses an obvious risk in such patients, can increase the severity of osteoarthritis and contribute to the development of complications [10]. Under physiological conditions, free radicals take part in the regulation of cellular signaling, aging and apoptosis of chondrocytes, in the synthesis and degradation of the extracellular matrix, and under pathological conditions - in the development of synovial inflammation and dysfunction of the subchondral bone. Therefore, one of the aspects of the pathogenesis of osteoarthritis is a violation of the oxidative-antioxidant balance and the development of oxidative stress [11].

Thus, to date, the issue of the risks of infection with the coronavirus disease, which causes the development of numerous adverse consequences and provocation of concomitant diseases, remains understudied. In particular, this applies to rheumatic and inflammatory lesions of the joints (for example, osteoarthritis) under conditions of coronavirus infection. Thus, according to clinical information, an increasing number of cases of joint damage develop in patients after COVID-19, which makes this condition worthy of further study [12-14].

The aim of the work.

To determine a number of indicators of the oxidant-antioxidant balance in the synovial fluid of patients with osteoarthritis after SARS-CoV2 infection.

Object and research methods.

The study involved 36 patients aged 39 to 70 years who were undergoing inpatient or outpatient treatment at the orthopedic specialized medical center «Ortoklinika» (Ternopil, Ukraine) for osteoarthritis. Patients

were diagnosed with «osteoarthritis of the knee joints of the II-III degree» on the basis of clinical and radiological criteria. At the stage of selection, all patients underwent radiography of the knee joints in direct (anterior-posterior) and lateral projections. The assessment of the intensity of pain and the functional state of the knee joints of the patients was carried out using the calculation of the WOMAC index (Western Ontario and McMaster Universities Osteoarthritis Index), which is calculated as a result of the patient's self-passing of the test, which includes 24 questions reflecting the severity of pain sensations (5 questions), stiffness (2 questions) and functional activity (17 questions) [15].

All study participants were further divided into the following groups. The first group (n=22) is patients with osteoarthritis of knee joints II-III degree. The second group (n=14) is patients with osteoarthritis of the knee joints II-III degree, who suffered a mild and moderate form of COVID-19 6-9 months ago. The diagnosis of COVID-19 was confirmed by molecular analysis (RT-PCR) of a nasopharyngeal swab. All participants who voluntarily agreed to participate in this study read and signed the appropriate informed consent form. The research was carried out in compliance with the main provisions of the «Rules of Ethical Principles of Conducting Scientific Medical Research with Human Participation», approved by the Declaration of Helsinki (1964-2013), ICH GCP (1996), EU Directive № 609 (from November 24, 1986), orders of the Ministry of Health of Ukraine № 690 dated 23.09.2009, № 944 dated 14.12.2009, № 616 dated 03.08.2012 and approved by the Ethics Committees of the Orthoclinic Medical Center (Ternopil, Ukraine) and the Educational and Scientific Center «Institute of Biology and Medicine» of Taras Shevchenko Kyiv National University (Kyiv, Ukraine). All measures are taken to ensure patient anonymity.

The collection of biological material was carried out on the basis of the specialized medical center «Orthoklinika», the city of Ternopil, Ukraine. Synovial fluid was collected in sterile heparinized tubes by arthrocentesis of the knee joint according to standard processing protocols. Given that the largest cavities of the knee and hip joints have a maximum volume of synovial fluid of up to 3.5 ml, taking biological material from otherwise healthy people is dangerous and may lead to a violation of the structural and functional state of the joint. In this regard, there is no group of conditionally healthy people in the research.

The following parameters were determined in the synovial fluid: the concentration of superoxide radical and hydrogen peroxide and the enzymatic activity of superoxide dismutase and catalase. The content of the superoxide radical was determined by the formation of CTT formazan [16]. The content of hydrogen peroxide was measured in the sorbitol-xylene orange system [17]. Superoxide dismutase (SOD) activity was determined by the ability of SOD to compete with nitroblue tetrazolium for superoxide radicals [18]. Catalase activity was measured by the amount of intact hydrogen peroxide in the sample [19]. The obtained data were tested for normal distribution using the Shapiro-Wilk test using the software package «GraphPad Prism 8.4.3» (GraphPad Software Inc., USA). Further calculation of the results was carried out using the Kruskal-Wallis H-test with Dunn's post test. The obtained results are shown as the

arithmetic mean \pm standard error of the mean. Results were considered significant when $p \leq 0.05$.

Research results and their discussion.

Synovial fluid is an important component of the joint, which is located between the articular cartilage and the synovial membrane. By its structure, it is a viscous liquid that performs lubricating, metabolic and regulatory functions in the joints. In its composition, synovial fluid contains lubricating molecules, including proteoglycan-4 and hyaluronan. Synovial fluid is an ultrafiltrate of blood plasma, which contains various cell populations: monocytes, lymphocytes, neutrophils, synovial cells, and macrophages of synovial origin. Maintaining the normal composition and function of synovial fluid is important for joint homeostasis. Changes in its composition and function are observed in osteoarthritis, rheumatoid arthritis, and joint damage. Thus, the study of the biochemical parameters of the state of the synovial fluid is necessary for understanding the development of pathological changes in the joint, establishing the stage of the disease and monitoring the effectiveness of the treatment of joint diseases.

Indicators of oxidative-antioxidant balance occupy an important place among such criteria. It is known that in the synovial environment of the joint, free radical processes play a significant role in the development of the inflammatory response, lipoperoxidation, cartilage degradation and chondrocyte death. Excessive formation of free radicals is associated with a malfunction of the antioxidant protection system, in which the enzymatic chain plays an important role [11, 20]. In our research, we evaluated the intensity of free radical processes in the synovial fluid of patients with osteoarthritis after SARS-CoV2 infection by the concentration of reactive oxygen species (superoxide radical, hydrogen peroxide) and the activity of enzymes of the first line of defense against free radicals (superoxide dismutase and catalase).

In the course of our research, it was established that in a group of patients with osteoarthritis of the knee joints, the content of superoxide radical in the synovial fluid is $0.37 \pm 0.03 \mu\text{mol}$ of XTT-formazan \times mg of protein-1 (**table 1**). When studying the content of this indicator in the synovial fluid of the joints of a group of patients with osteoarthritis who contracted COVID-19, the content of superoxide radical increases by 1.6 times compared to the group of patients with osteoarthritis (**table 1**). It was shown that the content of hydrogen peroxide in the synovial fluid of patients with osteoarthritis is $0.19 \pm 0.01 \mu\text{mol}$ \times mg of protein-1 (**table 1**). When assessing the concentration of the studied indicator in the synovial fluid of the joints of patients with osteoarthritis who suffered from a mild and moderate form of COVID-19, the content of hydrogen peroxide increases by 1.8 times compared to the group of patients with osteoarthritis (**table 1**).

Antioxidant enzymes play an important role in neutralizing free radicals. The enzymes superoxide dismutase and catalase are the first line of antioxidant protection of the body against free radicals [20]. Superoxide dismutase catalyzes the dismutation reaction of superoxide anions and maintains their concentration at a fairly low level. The biological value of catalase lies in the decomposition of hydrogen peroxide into water and molecular oxygen. Thanks to the joint work of these antioxidant enzymes, the level of free radicals is

maintained at a physiological level. These indicators are important parameters for assessing the intensity of free radical processes in the body [20].

When evaluating the enzymatic link of antioxidant protection, we found that the superoxide dismutase activity in the synovial fluid of a group of patients with osteoarthritis is equal to 1.99 ± 0.17 c.u. \times min⁻¹ \times mg protein⁻¹ (table 2). It was established that the enzymatic activity of this indicator in the synovial fluid of the joints of patients with osteoarthritis who contracted COVID-19 is reduced by 1.4 times compared to the group of patients with osteoarthritis (table 2). It was shown that in the synovial fluid of patients with osteoarthritis, catalase activity is 5.38 ± 0.51 μ mol \times min⁻¹ \times mg protein⁻¹ (table 2). During the experimental studies, it was found that in the synovial fluid of the joints of patients with osteoarthritis who suffered from COVID-19, catalase activity decreases by 1.6 times compared to the group of patients with osteoarthritis (table 2).

Our results indicate the excessive formation of free radicals - superoxide radical and hydrogen peroxide, which are reactive compounds belonging to reactive oxygen species (ROS). The biological effects of free radicals are concentration-dependent: at low concentrations, they manifest themselves as signal molecules (for example, hydrogen peroxide), and at high concentrations - as a cytotoxic oxidant [21, 22]. The biological effects of the above-mentioned oxygen intermediates are realized indirectly - through the strengthening of the oxidation processes of biological molecules: lipids, proteins, nucleic acids. In particular, ROS can directly or indirectly damage the main articular components and lead to clinical manifestations of inflammatory arthritis. Thus, the hydrogen peroxide molecule, which diffuses well, easily suppresses the synthesis of cartilage proteoglycans. This can happen in several ways: by interfering with ATP synthesis, partially by inhibiting the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase in chondrocytes, enhancing the effects of proteolytic and free radical-mediated cartilage degradation. In addition to their own damaging effect, the superoxide radical and hydrogen peroxide are precursors to the formation of a strong oxidant - the hydroxide radical, a product of the three-electron reduction of oxygen, which damages biological molecules. In joints, hydroxyl radicals break down isolated proteoglycans and fragment collagen. Thus, in the affected joint, free radicals contribute to the progression of joint damage [23, 24].

Other researchers also confirm a violation of the oxidative-antioxidant balance in patients with osteoarthritis. According to literature data [25, 26], an increase in the formation of free radicals, such as hydrogen peroxide and nitric oxide, was found in the synovial fluid of patients with osteoarthritis. At the same time, an excessive concentration of malondialdehyde, which is a secondary product of lipid peroxidation, was observed. It was also shown that the activity of antioxidant enzymes such as superoxide dismutase, catalase, glutathione-S-transferase and glutathione peroxidase decreases in the synovial fluid of patients with osteoarthritis against the back-

Table 1 – The content of reactive oxygen species in the synovial fluid of the knee joints of the experimental groups, (M \pm m)

Groups Indicator	Osteoarthritis (n=22)	Osteoarthritis + COVID-19 (n=14)
Superoxide anion radical, μ mol of XTT-formazan \times mg of protein ⁻¹	0.37 \pm 0.03	0.61 \pm 0.05*
Hydrogen peroxide, μ mol \times mg protein ⁻¹	0.19 \pm 0.01	0.34 \pm 0.03*

Notes: * – p < 0.05 relative to the group of people with osteoarthritis.

ground of a decrease in the concentration of reduced glutathione. The researchers also established a correlation between the severity of the pathological process in the joint and the intensity of free radical processes in the synovial fluid of patients with osteoarthritis. Scott sang. studied the importance of superoxide dismutase inside and outside chondrocytes in the regulation of ROS in cartilage [27]. They showed that the expression of superoxide dismutase is reduced in the cartilage of patients with progressive osteoarthritis. This, in turn, further increased the response to oxidative stress in chondrocytes and contributed to chondrocyte degeneration. In turn, Regan sang. found that extracellular superoxide dismutase also plays an important role in the regulation of ROS in cartilage. They found that under conditions of osteoarthritis, its activity decreases, which contributes to the development of osteoarthritis [28]. Polish scientists studied antioxidant enzymes in the whole blood of people with osteoarthritis of the knee joint and established a decrease in the enzymatic activity of superoxide dismutase, catalase, and glutathione peroxidase [29]. Therefore, the imbalance between the formation of free radicals and the endogenous mechanisms of antioxidant protection causes oxidative modification of the main cellular components, which is the basis for the genesis of osteoarthritis.

In addition, the intensification of free radical processes is directly related to inflammatory processes in the joint [30]. Inflammatory mediators such as interleukin-1 β , tumor necrosis factor- α , and interleukin-6 are highly activated in osteoarthritis joints. They induce the production of ROS and the expression of matrix proteases, which leads to the degradation of the extracellular matrix of cartilage and joint dysfunction. In turn, the formed organic peroxides increase swelling and the production of prostaglandins, which increases the development of inflammation [31]. ROS and inflammation are interdependent processes and each is a target of the other. Thus, literature data indicate a relationship between excessive free radical formation and the development of inflammation in osteoarthritis, which mediates local tissue reactions between joint components. Thus, oxidative stress not only contributes to the

Table 2 – Antioxidant enzymes activity in the synovial fluid of the knee joints of the experimental groups, (M \pm m)

Groups Indicator	Osteoarthritis (n=22)	Osteoarthritis + COVID-19 (n=14)
Superoxide dismutase activity, unit \times min ⁻¹ \times mg protein ⁻¹	1.99 \pm 0.17	1.38 \pm 0.12*
Catalase activity, μ mol \times min ⁻¹ \times mg protein ⁻¹	5.38 \pm 0.51	3.34 \pm 0.32*

Notes: * – p < 0.05 relative to the group of people with osteoarthritis.

destruction of cartilage, but also participates in the inflammatory transformation, contributing to the transition from clinically hidden cartilage destruction to the overt manifestation of clinical symptoms of osteoarthritis. Considering the results we obtained, it is important to further study the course of osteoarthritis in patients who have suffered from COVID-19.

Conclusions.

In the course of our experimental studies in the synovial fluid of osteoarthritis patients who contracted COVID-19, a violation of the oxidative-antioxidant balance with excessive formation of ROS and a decrease in the activity of antioxidant protection enzymes was found in the synovial fluid. This, in turn, increases local intra-articular damage and subsequent synovial inflammation, which leads to cartilage degradation. Our results indicate that patients with osteoarthritis may experience a more severe course of osteoarthritis and develop complications after infection with COVID-19.

Prospects for further research.

Despite the fact that since the beginning of the COVID-19 pandemic, many steps forward have been made in understanding the pathogenicity of the virus, there are still many unexplored aspects of the course of this disease and the long-term consequences associated with SARS-CoV2 infection. Research into the pathogenesis of coronavirus infection in patients with chronic diseases, particularly osteoarthritis, requires careful study. Therefore, complete clinical and laboratory data, careful observation of the patient and the study of the mechanisms of pathogenesis are of paramount importance for conducting a personalized thorough differential diagnosis and clearly defining the signs of joint damage associated with SARS-CoV2 infection. On the basis of a complete picture of the disease, optimal treatment regimens can be created, which will help to slow down the development of a more severe course of osteoarthritis as much as possible and prevent its complications.

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ПОКАЗНИКИ ОКИСНО-АНТИОКСИДАНТНОЇ СИСТЕМИ У СИНОВІАЛЬНІЙ РІДИНІ ХВОРИХ НА ОСТЕОАРТРИТ ПІСЛЯ SARS-CoV2-ІНФЕКЦІЇ

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Резюме. Коронавірусна хвороба 2019 року (Coronavirus disease 2019, COVID-19) є пандемічним захворюванням XXI століття, що вражає людську популяцію. Це респіраторне захворювання, що характеризується розвитком важких ускладнень небезпечних для життя людини. Часто розвиток ускладнень спостерігається у пацієнтів з COVID-19, що були похилого віку або мали інші основні захворювання. Серед таких пацієнтів з хронічними захворюваннями важливу групу складають хворі з патологією опорно-рухової системи, зокрема остеоартритами. Згідно даних клінічних досліджень все більша кількість випадків ураження суглобів розвивається у пацієнтів після COVID-19, що робить цей стан вартим для подальшого вивчення. Порушення окисно-антиоксидантного балансу та розвиток окисного стресу відіграє важливе значення у патогенезі остеоартритів. Метою роботи було визначити ряд показників окисно-антиоксидантного балансу у синовіальній рідині хворих на остеоартрит після SARS-CoV2-інфекції. Всі учасники дослідження були поділені на дві групи. Перша група (n=22) – пацієнти з остеоартритом колінних суглобів II–III ступеню. Друга група (n=14) – пацієнти з остеоартритом колінних суглобів II–III ступеню, які перенесли легку та середньотяжку форму COVID-19 6-9 місяців тому. У проведених дослідженнях проводилась оцінка концентрації супероксидного радикалу та гідроген пероксиду, супероксиддисмутази та каталази ферментативних активностей у синовіальній рідині пацієнтів всіх дослідних груп. Концентрацію супероксидного радикалу визначали за утворенням ХТТ-формазану. Концентрацію гідроген пероксиду вимірювали у системі сорбітол-ксиленол оранж. Супероксиддисмутазу (СОД) активність визначали за здатністю СОД конкурувати із нітросинім тетразолієм за супероксидні радикали. Каталазну активність вимірювали за кількістю незруйнованого пероксиду водню у пробі. Обробку результатів дослідження проводили загальноприйнятими методами варіаційної статистики.

Встановлено, що у синовіальній рідині пацієнтів з остеоартритом колінних суглобів, які перехворіли COVID-19, збільшується концентрація супероксидного радикалу – в 1,6 раза та гідроген пероксиду – в 1,8 раза порівняно з групою хворих на остеоартрит. Виявлено, що у синовіальній рідині суглобів пацієнтів з остеоартритом, які перехворіли COVID-19, знижується активність супероксиддисмутази – в 1,4 раза та каталази – в 1,6 раза відносно групи хворих на остеоартрит. Виявлені зміни свідчать про порушення окисно-антиоксидантної рівноваги з надмірним утворенням активних форм кисню та зниженням активності ферментів антиоксидантного захисту. Це вказує на превалювання вільнорадикальних процесів та розвиток окисного стресу безпосередньо в суглобі. Отримані нами результати свідчать, що у хворих на остеоартрит після інфікування COVID-19 можливий більш важкий перебіг остеоартриту та розвиток ускладнень.

Ключові слова: SARS-CoV-2, остеоартрит, синовіальна рідина, вільнорадикальні процеси, антиоксидантна система.

INDICATORS OF THE OXIDANT-ANTIOXIDANT SYSTEM IN THE SYNOVIAL FLUID OF PATIENTS WITH OSTEOARTHRITIS AFTER SARS-CoV2 INFECTION

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Abstract. The 2019 coronavirus disease (Coronavirus disease 2019, COVID-19) is a pandemic disease of the 21st century that affects the human population. This is a respiratory disease characterized by the development of serious complications that are dangerous for human life. Often, the development of complications is observed in patients with COVID-19 who were elderly or had other underlying diseases. Among such patients with chronic diseases, patients with pathologies of the musculoskeletal system, particularly osteoarthritis, are an important group. According to clinical research data, an increasing number of cases of joint damage develop in patients after COVID-19, making this condition worthy of further study. Violation of the oxidant-antioxidant balance and the development of oxidative stress play an important role in the pathogenesis of osteoarthritis. The aim of the work was to determine a number of indicators of the oxidant-antioxidant balance in the synovial fluid of patients with osteoarthritis after SARS-CoV2 infection. All study participants were divided into two groups. The first group (n=22) is patients with osteoarthritis of knee joints II-III degree. The second group (n=14) is patients with osteoarthritis of the knee joints II-III degree, who suffered a mild and moderate form of COVID-19 6-9 months ago. In the conducted studies, the concentration of superoxide radical and hydrogen peroxide and the enzymatic activity of superoxide dismutase and catalase in the synovial fluid of patients of all experimental groups were evaluated. The content of the superoxide radical was determined by the formation of XTT formazan. The content of hydrogen peroxide was measured in the sorbitol-xylene orange system. Superoxide dismutase (SOD) activity was determined by the ability of SOD to compete with nitroblue tetrazolium for superoxide radicals. Catalase activity was measured by the amount of intact hydrogen peroxide in the sample. Processing of research results was carried out using generally accepted methods of variational statistics.

It was established that in the synovial fluid of patients with osteoarthritis of the knee joints who contracted COVID-19, the content of superoxide radical increased by 1.6 times and hydrogen peroxide by 1.8 times compared to the group of patients with osteoarthritis. It was found that in the synovial fluid of the joints of patients with osteoarthritis who fell ill with COVID-19, superoxide dismutase activity is reduced by 1.4 times and catalase activity by 1.6 times compared to the group of patients with osteoarthritis. The detected changes indicate a violation of the oxidative-antioxidant balance with excessive formation of reactive oxygen species and a decrease in the activity of antioxidant protection enzymes. This indicates the prevalence of free radical processes and the development of oxidative stress directly in the joint. The results obtained by us indicate that patients with osteoarthritis may have a more severe course of osteoarthritis and the development of complications after infection with COVID-19.

Key words: SARS-CoV-2, osteoarthritis, synovial fluid, free radical processes, antioxidant system.

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The authors of the paper confirm the absence of conflict of interest.

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