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Assessment of the Immune and Oxidative Status of Patients with Osteoarthritis

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Abstract Assessment of systemic and local changes in the immune and oxidative status of patients with osteoarthritis, depending on different age groups, has shown that the prognostic significance of the information obtained, which is highly reliable, makes it possible to choose the right treatment method and, accordingly, reduce the number of complications and disability among patients with osteoarthritis.

Keywords Osteoarthritis, Immune-oxidant status, Prognosis

1. Introduction

According to some researchers, 10 to 12% of the world's population suffers from osteoarthritis (OA) [1,2,6], others indicate higher rates - up to 20% [3,4,7,8]. Among all orthopedic diseases for which patients consulted a doctor, 55% is arthroarthritis [5,9,21,22]. In the structure of degenerative and dystrophic joint diseases, one third is in the knee joint and reaches 33.3% of cases, and every third patient has both knee joints affected [10,11,23,24]. According to Russian researchers, the incidence of osteoarthritis of the knee joint per 10,000 inhabitants of Russia is 99.6 cases [4,25]. The proportion of osteoarthritis among diseases of the musculoskeletal system that caused disability reaches 16,5% [7,12,13]. Osteoarthritis of the knee joint leads to a significant decrease in working capacity and disability of people of working age from 8 to 21% of cases [14,16,26,27]. Rheumatoid arthritis and deforming osteoarthritis account for 13.2% of people with disabilities with diseases of the musculoskeletal system. On average, one out of every 100 patients suffering from diseases of the musculoskeletal system becomes disabled [17,30]. A significant decrease in the quality of life of people with disabilities is caused by pain syndrome, restriction of freedom of movement and loss of functional activity, and sometimes the ability to self-serve [12,14,18,28,29]. Osteoarthritis is far ahead of gastrointestinal, respiratory and cardiovascular diseases in terms of reducing the quality of life of patients. Along with coronary heart disease, alcoholism, depression and diabetes, osteoarthritis of the joints is among the factors most often responsible for long-term health problems. AA has a negative psychological and economic impact not only on those who suffer from it, but also on their loved ones, as well as on society as a whole. This is especially true if the patient is at a young and able-bodied age [19,20].

The human antioxidant system (AOS) is a mechanism that prevents the formation of highly active free radicals, i.e. reactive oxygen species [13,18,19]. Under normal physiological conditions, small amounts of oxygen are constantly converted into superoxide anions, hydrogen peroxide, and hydroxyl radicals. Excessive formation of these radicals can lead to cell damage, and the antioxidant system works as a compensatory mechanism to neutralize their effects.

One of the key AOS enzymes is superoxide dismutase (SOD), which acts as the first line of defense. This enzyme is present in cells that consume oxygen. Its main function is to accelerate the reaction that converts the superoxide radical, which is toxic to the body, into hydrogen peroxide and molecular oxygen.

Assessment of the overall antioxidant status allows the doctor to more accurately assess the condition of the body, to identify possible reserves of protection both in normal physiological conditions and in various pathological conditions.

Malonic dialdehyde (MDA) is an endogenous aldehyde formed as a result of the metabolism of arachidonic acid and other polyunsaturated fatty acids. As a result of further biochemical transformations, it is oxidized to carbon dioxide or interacts with phospholipids, amino acids and nucleic

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acids. Currently, malondialdehyde is considered as a marker of lipid peroxidation and oxidative stress.

Determining the overall antioxidant status helps the clinician to better assess the state of the body, the observed and its potential protective reserves in certain physiological and pathological conditions.

It should be noted that we have not found any data on the direction of immune activity and antioxidant status of AA patients, taking into account the age group, in the available literary and electronic sources of information.

All of the above has determined the main direction of this work.

The aim of the study was to develop and implement a methodology for determining immune and oxidative status in young and middle-aged patients with osteoarthritis.

2. Materials and Methods

96 patients with osteoarthritis who underwent inpatient treatment at the clinic of the National Center for Rehabilitation and Prosthetics of Persons with Disabilities under the National Agency for Social Protection under the President of the Republic of Uzbekistan in 2022-2024 were examined. The patients were included in the study using a continuous sampling method.

All 96 examined patients were divided into 2 study groups, according to the age criterion, since the main purpose of the work was to identify the features of the course of AA in young patients, and for comparison we took middle-aged AA patients. Thus, group 1 included 52 young people (from 18 to 44 years old), who accounted for 54.2% of the total number of patients examined, group 2, respectively, included 44 middle-aged people (from 45 to 59 years old), who accounted for 45.8% of the total number of patients included in the study.

Next, we examined the distribution of all examined patients according to age and gender characteristics.

The duration of the disease in the examined patients ranged from 2 weeks to several months (the average duration was 29.9±5.7 days).

The clinical study of patients with AA included the collection of complaints and anamnesis, examination using palpation, percussion, auscultation, measurement of anthropometric parameters (height, body weight, body mass index). All patients underwent general blood and urine tests, a biochemical blood test, and a coagulogram. Serological markers of viral hepatitis B and C (HBsAd, AHBs, aHCV) were determined by enzyme immunoassay. Instrumental methods included joint radiography, joint arthroscopy, ultrasound examination of the abdominal cavity and kidneys, and ECG.

All clinical and anamnestic and instrumental laboratory data were entered into a developed individual questionnaire, which noted complaints and objective data characteristic of joint syndrome and extra-articular manifestations, anamnestic information about this disease and other diseases, smoking, alcohol consumption, medications, etc.

Also, upon admission to the hospital, all patients underwent clinical and laboratory tests, including a general blood test with a coagulogram, determining the number of leukocytes, lymphocytes, monocytes, granulocytes (absolute and relative numbers), lymphocytes, hemoglobin, erythrocytes, average volume of erythrocytes, platelets, thrombocrit, large platelets, ESR, C-reactive protein, ADC, prothrombin time, values of the prothrombin index, APTT, fibrinogen, INR, as well as indicators of general urinalysis.

Patients with AA underwent knee joint radiography in two standard projections using an Apelem Baccara 90/20 digital device with an assessment of radiological stages.

The radiological stage (according to Steinbroker) was determined by the following criteria:

stage 0 – absence of radiological signs in the presence of clinical manifestations (pain, local fever, swelling after heavy exertion);

Stage I – doubtful – minor osteophytes, narrowing of the articular gap is not determined or minimal; (N.B. Formally, according to the latest protocols for the diagnosis and treatment of osteoarthritis, the presence of osteophytes and narrowing of the articular gap, together with clinical manifestations, entitles an orthopedic traumatologist to diagnose osteoarthritis);

Stage II - minimal - small osteophytes on the edges of the articular the appearance of marginal bone growths of articular surfaces, a slight narrowing of the articular gap is determined;

Stage III – moderate (moderate changes) – moderate narrowing of the articular fissure (in most cases predominates on the medial side); multiple small or moderate osteophytes on the edges of the articular surfaces; minor subchondral osteosclerosis, especially pronounced at the site of the greatest narrowing of the articular fissure; minor deformities of the articular surfaces;

Stage IV – pronounced (pronounced changes) – pronounced narrowing of the articular fissure to complete absence; multiple osteophytes; pronounced subchondral osteosclerosis; significant deformities of the epiphyses of the bones forming the joint.

Joint functional insufficiency (FNS) was divided into 3 classes and evaluated using the following criteria:

I – self-care (dressing, eating, self-care, etc.), non-professional (elements of leisure, recreation, sports, etc.) and 60 professional activities (study, work, housekeeping for housekeepers) are preserved;

II – self-service and professional activities are preserved, non-professional activities are limited;

III – self-service is maintained, non-professional and professional activities are limited;

IV – self-service, non-professional and professional activities are limited. At the time of inclusion in the study, all patients were receiving drug therapy, taking into account the activity of the disease and the tolerability of drugs.

Evaluation of the effectiveness of the therapy used included: the dynamics of clinical and laboratory parameters, the nature of the course, and the possibility of achieving remission.

The serum concentrations of immunoglobulins of the main classes A, M, G, E and secretory immunoglobulin A were determined by solid-phase enzyme immunoassay

(ELISA) using the test systems of Vector Best JSC (Russia) according to the attached instructions. The results of studies of immunoglobulins of the main classes A, M, G, E were expressed in micrograms/ml, the level of secretory immunoglobulin A was expressed in ng/ml.

To determine the level of oxidative stress in the body, the activity of lipoperoxidation was assessed by changes in the concentration of malonic dialdehyde (MDA) in blood serum by reaction with thiobarbituric acid and by the content of superoxide dismutase (SOD). SOD was determined by enzyme immunoassay on a Human Reader HS analyzer (Germany) using ELISA-SOD test systems (Cytokin LLC, St. Petersburg, Russia). The coefficient of variation of the results of 10 SOD determinations in the same sample using a set does not exceed 10%. Sensitivity – the minimum reliably determined concentration of SOD in the studied samples does not exceed 100 pg/ml.

The results and their discussion. In recent years, researchers have begun to pay attention to the problem of disorders and regulation of immune mechanisms observed in AA. There is information about the activation of chondrocytes in cartilage tissue with the release of pro-inflammatory cytokines, metalloproteinases. However, the results of studies on the characteristics of the immune status in synovial fluid, which is one of the main organ-specific components of the joint that determine its functional state, are still few and rather contradictory. But it is especially the local, in particular humoral immune status that determines the course and prognosis of the inflammatory process in the joint.

The levels of total immunoglobulins A, M, and G in the blood serum of OA patients did not significantly differ from those of the control group and even tended to decrease slightly. The levels of large and small circulating immune cells (3% and 4%) (CIC 3% and CIC 4%) in the blood serum of AA patients of both age groups had no significant differences from the control group.

It is noteworthy that the level of total immunoglobulins A, M, and G in the synovial fluid of OA patients was higher than in the control group. And if the indicators of total immunoglobulins A, M, and G in the synovial fluid of young OA patients had only an unreliable tendency to increase relative to the control group, then in the group of middle–aged patients these differences were significant and the level of total IgA was 1.36 times higher than the control indicators, the level of total IgM was 1.97 times higher, and The level of total IgG is 2.41 times.

A comparative analysis of the parameters of immunoglobulin E (IgE) and secretory immunoglobulin A (sIgA) in the blood serum and synovial fluid of OA patients, as more locally acting immunoglobulins, aroused greater interest.

It was revealed that in the blood serum of patients both in the general sample and in individual age groups, IgE had no significant differences from the indicators of the control group, while analyzing its level in the synovial fluid, significant differences were revealed, which is natural, since IgE, unlike other immunoglobulins, has a higher cytophilicity. IgE attaches its Fc fragment to the receptors of mast cells, basophils and eosinophils, and when bound to antigens causes mast cell degranulation and the release of granules of histamine and other mediators. On the one hand, mediators attract eosinophils and some other cells to the degranulation site and mobilize them, and on the other hand, they change the permeability of capillaries and create conditions for the entry of antibodies and effector cells into tissues, thereby leading to the development of immediate hypersensitivity. As we can see, its level in the synovial fluid of patients in group 1 is 1.38 times higher than in the control group, while in patients in group 2 this difference is 2.21 times. This suggests that in middle-aged patients, the development of inflammatory phenomena in the joint is largely due to immediate-type hypersensitivity mechanisms.

Secretory immunoglobulin A (sIgA) performs the function of local specific immune protection and plays an important role in local homeostasis. sIgA is active against a variety of antigens and prevents their penetration through the mucous membranes into deeper tissues. Secretory immunoglobulin A is produced by B lymphocytes located near the cells of the mucous membrane, and then transported and released through specific cellular mechanisms of epithelial cells into the intracavitary secretion, therefore, when examining local sIgA, it is possible to evaluate the immune defense of both local and systemic levels.

When conducting a correlation analysis between the level of local sIgA and indicators reflecting the functional state of the body in groups 1 and 2, different correlations were revealed. In group 1: with leukocytes ($r=0.96$), monocytes ($r=0.84$), hemoglobin ($r=0.95$), CRP in synovial fluid ($r=0.89$). In group 2: with thrombocrit ($r=0.91$), prothrombin time ($r=0.60$), INR ($r=0.62$). It was also found that the sIgA level had a strong inverse relationship with the duration of the inflammatory process in the joint in patients of group 2 ($r=-0.77$, $p<0.005$).

The human antioxidant system (AOS) is a mechanism that prevents the formation of highly active free radicals, that is, reactive oxygen species. Under normal physiological conditions, small amounts of oxygen are constantly converted into superoxide anions, hydrogen peroxide, and hydroxyl radicals. Excessive formation of these radicals can lead to cell damage, and the antioxidant system works as a compensatory mechanism to neutralize their effects. Assessment of the overall antioxidant status allows the doctor to more accurately assess the condition of the body, to identify possible reserves of protection both in normal physiological conditions and in various pathological conditions.

One of the key AOS enzymes is superoxide dismutase (SOD), which acts as the first line of defense. This enzyme is present in cells that consume oxygen. Its main function is to accelerate the reaction that converts the superoxide radical, which is toxic to the body, into hydrogen peroxide and molecular oxygen.

Malonic dialdehyde (MDA) is an endogenous aldehyde formed as a result of the metabolism of arachidonic acid and other polyunsaturated fatty acids. As a result of further biochemical transformations, it is oxidized to carbon dioxide

or interacts with phospholipids, amino acids and nucleic acids. Currently, malondialdehyde is considered as a marker of lipid peroxidation and oxidative stress.

It should be noted that we have not found any data on the direction of immune activity and antioxidant status of OA patients, taking into account the age group, in the available literary and electronic sources of information. Determining the overall antioxidant status helps the clinician to better assess the state of the body, the observed and its potential protective reserves in certain physiological and pathological conditions.

An important factor in the pathogenesis of AA is the imbalance between the production of reactive oxygen species (ROS) and the antioxidant system. Elevated levels of ROS in synovial fluid and cartilage tissue lead to damage to lipids, proteins, and DNA, increasing joint degeneration.

To identify the significance of changes in the state of oxidative stress at the local and systemic levels, we determined the content of superoxide dismutase (SOD) and malondialdehyde (MDA) in the synovial fluid and blood serum of OA patients in groups 1 and 2 compared.

The mechanism of action of superoxide dismutase (SOD) in OA is that this enzyme catalyzes the conversion of superoxide anion radical (O_2^-) into hydrogen peroxide (H_2o_2) and molecular oxygen (o_2), reducing the level of reactive oxygen species (ROS). This reduces oxidative damage to cells, protecting cartilage tissue from degradation. In OA, reactive oxygen species stimulate inflammatory processes, damage chondrocytes and the extracellular matrix. SODA reduces the concentration of superoxide radicals, slowing down oxidative damage and destruction of joint tissue.

In patients with OA of both age groups, there is a decrease in the activity of the antioxidant enzyme superoxide dismutase in the blood serum (to 781.6±150.84 pg/ml in young patients and to 494.2±90.52 pg/ml in middle-aged patients) compared with the indicator of the control group (934.2±76.4pg/ml), which indicates a decrease in the antioxidant properties of the body, moreover, in middle-aged patients this difference was significantly lower by 1.9 times ($p<0.05$) compared with a decrease of 1.2 times in young patients.

However, the nature of changes in SOD levels in the synovial fluid was different. In young patients, we also see a 1.4-fold decrease in SOD levels (to 638.3±126.2pg/ml) compared with the control group (897.5±61.8pg/ml). And in middle-aged patients, we see the opposite picture - a 1.2-fold increase in SOD levels compared to the control group. This shows differences in the mechanism of action of oxidative stress depending on the age of the patients. It is interesting to note that in both cases, changes in SOD levels are the cause of the development of pathological processes, however, in young patients due to insufficient protection from reactive oxygen species, and in middle-aged patients as a result of increased cytotoxic effects of H2O2 formed during O2 dismutation. That is, although at the systemic level the mechanism of oxidative stress disorder has a general character, at the local level each age period is characterized by a specific mechanism of action of SOD.

Malonic dialdehyde (MDA) is formed as a result of lipid peroxidation and is used as a marker of oxidative stress.

In AA patients in both age groups, we see an increase in MDA levels at both the systemic and local levels. Thus, the level of MDA in the blood serum in young patients was 4.9 times (10.64±1.7 mmol/ml), and in middle-aged patients it was 5.8 times higher (12.68±1.29 mmol/ml) than in the control group (2.18±0.33 mmol/ml). In the synovial fluid, this process was less intense and was 3.9 times higher than in the control group (1.64±0.46 mmol/ml) in young patients (6.38±1.13 mmol/ml), and 4.5 times higher in middle-aged patients (7.43±1.27 mmol/ml). The increased level of MDA reflects the intense destruction of cell membranes caused by ROS. And high levels of MDA increase inflammatory processes in the joint tissue and accelerate cartilage degeneration, which exacerbates the course of OA.

The relationship between SOD and MDA is to maintain the balance of the antioxidant system, since a decrease in SOD activity leads to the accumulation of ROS, which enhances LPO processes and increases the level of MDA. This creates a vicious circle of oxidative damage that accelerates the progression of OA.

3. Conclusions

1. The level of total immunoglobulins A, M, and G in the synovial fluid of OA patients was higher than in the control group. The level of IgE in the synovial fluid of patients in group 1 is 1.38 times higher than in the control group, while in patients in group 2 this difference is 2.21 times. And as we can see, sIgA production is more pronounced in group 2 AA patients, in whom this indicator is significantly higher than in the control group by 2.41 times (P 0.05), while in group 1 patients it is only 1.43 times higher. Thus, the results of our research have shown that humoral immunoreactivity is more pronounced at the local level, especially in middle-aged arthroarthritis patients, apparently causing a more prolonged and recurrent course of the disease.
2. Metabolic and oxidative changes play a key role in the pathogenesis of osteoarthritis, increasing inflammation and degradation of joint tissue. An in-depth study of these processes may contribute to the development of new therapeutic approaches aimed at reducing oxidative stress and correcting metabolic disorders to improve the quality of life of patients with OA.

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