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The Role of Inflammatory Mediators in Patients with Osteoarthritis and Arterial Hypertension

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Abstract: Mediators of inflammation and the activity of lymphocyte-platelet adhesion were studied in 58 patients with osteoarthritis. The control group consisted of 16 practically healthy individuals. An increase in the concentration of proinflammatory cytokines (IL-1□, TNF□, IL-6) and an increase in the activity of lymphocyte-platelet adhesion in patients with osteoarthritis were established. A relationship was revealed between the level of pro-inflammatory cytokines and the degree of lymphocyte-platelet adhesion activity.

Keywords: osteoarthritis, endothelial dysfunction, cytokines.

Introduction. Osteoarthritis (OA) is the most common joint pathology among diseases of the musculoskeletal system. Studies of the pathogenetic mechanisms of OA conducted in recent years allow us to consider this disease as an inflammatory-degenerative process with the occurrence of inflammation in the cells of the synovial membrane, subchondral bone and cartilage tissue [9]. In affected joints, the role of effector of inflammation is played mainly by the cells of the synovial membrane. Macrophage-type synoviocytes secrete proteases and inflammatory mediators. IL-1β, TNFα, IL-6 are involved as the main inducers of destruction of joint tissues [7, 8]. The role of a regulatory cytokine that inhibits the production of IL-1 and reduces enzymatic degradation of tissue belongs to IL-4 [4]. Adhesive processes between platelets and leukocytes are the leading links in the mechanisms that ensure cell migration to the damaged area. Lymphocyte-platelet aggregates are directly involved in the course of local immunological and hemostatic reactions, as well as reparative processes aimed at restoring damaged tissues [14]. A number of studies have described the pathogenetic and clinical significance of lymphocyte-platelet adhesion (LTA) in various pathological conditions [2, 3], but similar studies of intercellular interaction in OA have not been conducted.

Chronic pain increases the activity of the thalamic centers of the brain and the secretion of catecholamines [1]. In turn, NSAIDs inhibit the synthesis of vasodilating prostaglandins, increase sodium reabsorption in the ascending loop of Henle and, therefore, reduce diuresis [6]. In addition, with OA, even without significant inflammatory process, moderate endothelial dysfunction is observed, accompanied by endotheliocythemia [12].

Materials and methods

58 patients with identified clinical and radiological signs of OA were examined. The first group consisted of 35 patients with OA with normal blood pressure, the second – 23 patients with OA in combination with hypertension. The control group was a group of 16 people without joint pathology and hypertension. This study was a study of the content of cytokines and LTA activity in the blood of OA patients with hypertension.

The patient groups were comparable by gender and age (Table 1). All persons included in the study gave informed consent to the manipulations. The work did not include patients with concomitant chronic diseases, including coronary artery disease, obesity, and diabetes mellitus.

Table 1. Clinical characteristics of patients with osteoarthritis

Indicators	1st group	2nd group
Number of patients	35	23
Age, years	38,3±7,2	42,5±2,2
Floor -women -men	 26 (74,3%) 9 (25,7%)	 20 (87%) 3 (13%)
Duration of OA, years	4,5±3,4	6,2±4,6
OA stage (according to I. Kellgren) Stage I Stage II Stage III	 10 (28,6%) 19 (54,3%) 6 (17,1%)	 2 (8,7%) 16 (69,9%) 5 (21,7%)
Blood pressure indicators SBP (mm Hg) DBP (mm Hg)	 120±8 75±5	 145±10 95±12

The majority of patients had OA of the knee joints (50%), radiologically stages II and III according to I. Kellgren. 23% of patients suffered from polyosteoarthritis. 25% of patients had a combination of arthrosis with osteochondrosis of various parts of the spine. Synovitis was diagnosed in 23% of cases.

Interleukins were determined by enzyme immunoassay using reagent kits for the quantitative determination of human interleukins in biological fluids of Vector-Best JSC.

Table 2. Indicators of cytokines and LTA in the blood of patients with osteoarthritis (median, 25th – 75th percentile)

Indicators	Control	1st group	2nd group
	n =16	n =35	n =24
LTA, %	8 (8-12)	22,5* (19-26,5)	28*, # (23-34)
IL-1β, pg/ml	14,7 (12,3-16,8)	19* (14,1-22,4)	23*, # (18,1-32,1)
TNFα, pg/ml	8 (7,1-9,6)	10* (8,5-12)	12,8*, # (11,7-14,3)
IL-6, pg/ml	12,3 (11,3-13,9)	15,6* (11,4-22,3)	22,6*, # (18,2-32,2)
IL-4, pg/ml	2,8 (1,6-3,6)	4,3* (2,4-6,2)	4,3* (3-5,8)

note. * – significance of differences compared to the control group: ($p < 0.05$); # – significance of differences compared to group 1 ($p < 0.05$).

To assess the functional state of immunocompetent cells, the LTA test was used according to the method proposed by Yu.A. Witkovsky et al (1999). The number of lymphocyte-platelet rosettes was counted in the Goryaev chamber after obtaining a total pool of lymphocytes by layering heparinized blood onto urographinficoll (density 1.077) and centrifuging at 1500

rpm for 40 minutes, after which the interphase ring was taken with a pipette.

The obtained data were processed by the method of variation statistics for unrelated observations using a software package

"Statistica 6". The distribution of almost all variation series did not obey the criteria of normality, so nonparametric statistics methods were used. Groups were compared in pairs using the Mann–Whitney test. Correlation analysis was performed using Spearman's rank correlation coefficient. Differences between groups were considered significant at $p < 0.05$.

Results and discussion

In the study, the levels of pro-inflammatory cytokines (IL-1β, TNFα, IL-6) were significantly increased in groups 1 and 2 compared to the control (Table 2). There was an increase in these indicators in the group of OA in combination with hypertension compared to those in OA with normal blood pressure levels. Realizing their effects, cytokines (IL-1β, IL-6) enhance the synthesis of matrix metalloproteinases (MMPs) and activate IL-1β –dependent chain of intracellular reactions. As a result, the key enzyme that mediates the synthesis of glucosamines is inactivated and the destruction of cartilage is enhanced [5]. IL-1β has the ability to modulate the level of neurotransmitter production and stimulate the sympathoadrenal system. TNFα promotes increased generation of free radicals and may be the cause of intensified processes of apoptosis of the vascular endothelium and inactivation of nitric oxide [12]. As a result, endothelium-dependent vascular relaxation is weakened. By regulating the inflammatory response, IL-1β, TNFα, IL-6 stimulate the proliferation of endothelial cells, attract blood cells to the site of inflammation, and enhance collagen synthesis by fibroblasts [10]. These effects cause the development of changes in the structure of the vascular wall, which may play a pathogenetic role in increasing blood pressure.

The ability of proinflammatory cytokines (IL-1β, TNFα, IL-6) to change the function of the vascular endothelium, modulate the level of neurotransmitter production and stimulate the sympathoadrenal system probably partially determines the development of hypertension in OA. It was also found that in all patients, compared with the control group, there was an increase in the concentration of the regulatory cytokine (IL-4). However, no statistically significant difference in IL-4 concentrations was found between groups 1 and 2. IL-4 in the pathogenesis of OA exerts anti-inflammatory effects by inhibiting the production of IL-1, reducing the level of NO and

NO synthase in chondrocytes, reducing enzymatic tissue degradation [5].

In both study groups, a significant increase in the degree of LTA was revealed, which indicates changes in cellular immunity [2,13]. When conducting a correlation analysis, a relationship was established between the concentration of proinflammatory cytokines (IL-1β, TNFα and the increase in adhesive interaction between lymphocytes and platelets in patients with OA. The correlation coefficients between the levels of IL-1β, TNFα and LTA in patients of group 1 were 0.634 and 0.637, 2nd group – 0.538 and 0.532, respectively.

Activated platelets, being on the surface of collagen, provide primary hemostasis and unfold the proenzyme cascade of blood coagulation. At the same time, the blood platelets increase their contact with lymphocytes (T-helpers) and stimulate them with the help of released IL-1 molecules. It is known that under the influence of the latter, the secretion of IL-2 is stimulated, in the presence of which the rosette-forming ability of helper-inducing cells with intact platelets increases 4 times [2]. This results in increased adhesive interactions between lymphocytes and platelets, reflecting increased LTA.

Conclusions. The study revealed an increase in the concentration of cytokines in the group of patients with OA, which indicates the presence of an inflammatory component in the pathogenesis of the disease. The presence of chronic inflammation may be one of the

pathogenetic factors in the occurrence and formation of hypertension in this group of patients. In both groups of patients, an increase in the number of lymphocyte-platelet aggregates was detected compared to the control, which indicates changes in cellular immunity. The LTA test for this pathology may be a nonspecific marker of the severity of inflammation.

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