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THE ROLE OF ENDOTHELIAL DYSFUNCTION IN THE DEVELOPMENT OF OSTEOARTHRITIS IN WOMEN DURING MENOPACTERIC PERIOD

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Abstract
Osteoarthritis is a pathological lesion of the joints, characterized by structural changes in the articular cartilage and subchondral bone, as well as overt or covert moderate synovitis. Osteoarthritis is a pressing medical and social problem for most countries in the world due to its high prevalence, which reaches about 25% of the population. This disease is most common among women and is one of the reasons for decreased ability to work and increased disability. In osteoarthritis, endothelial dysfunction is a component of microcirculatory disorders. Desquamated endothelial cells and vascular endothelial growth factor are the main indicators of damage to the microcirculatory bed. Under the influence of proinflammatory cytokines, homeostasis in the microcirculatory link is destabilized. A necessary element in diagnosing osteoarthritis is the detection of an early marker.

Keywords: Osteoarthritis, microcirculatory imbalance, nitric oxide, monocyte chemoattractant protein.

Introduction

Osteoarthritis (OA) is a pathological lesion of the joints, characterized by structural changes in the articular cartilage and subchondral bone, as well as overt or covert moderate synovitis. Osteoarthritis accounts for about 70% of rheumatic diseases. Therefore, it is the most common joint pathology and is a pressing

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medical and social problem for most countries in the world due to its high prevalence, which reaches about 25% of the population.

This disease is most common among women and is one of the reasons for decreased work capacity and increased disability [1-3].

Osteoarthritis is a multifactorial disease, since mechanical factors prevail over biological ones in the pathogenesis of development. Oscillation of anabolic and catabolic processes is an important mechanism in the human body, necessary for maintaining tissue integrity. Direct imbalance of this process can be observed with prolonged tissue decay, with a decrease in the body's ability to recover and lead to increased activation of the catabolic/anabolic cycle.

OA is diagnosed in women twice as often as in men. After 55 years, coxarthrosis is more common in men, and gonarthrosis in women. With an increase in the Quetelet index, the risk of developing OA increases by 2.1 times in women, and by 1.5 times in men. For women, obesity is a more significant risk factor for developing OA. [10; 11]

Other risk factors include excess body weight, old age, injuries, professional sports, and occupational hazards. Cytokine damage occupies a separate position in the structure of causes of OA development [3; 4].

Microcirculatory imbalance is one of the main mechanisms in joint diseases. Vascular endothelium is a monolayer of specialized cells of mesenchymal origin that lines the blood and lymphatic vessels of the heart cavity [10; 11]. In OA, endothelial dysfunction (ED) is a component of microcirculatory disorders, but its role has not been sufficiently considered [1; 2]. ED is accompanied by activation of vasoconstrictors that promote narrowing of blood vessels, which provide microcirculatory disorders [2].

Desquamated endothelial cells (DEC),Vascular endothelial growth factor (VEGF), a signaling protein produced by cells to stimulate vasculogenesis, is an important indicator of damage to the endothelial lining of blood vessels [4].

Nitric oxide is an unstable compound secreted by the vascular endothelium. This substance is considered a kind of vasodilator, an indicator of endothelial disorders [7; 10].

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Under the influence of proinflammatory cytokines, there is a disturbance of the balance in the vascular endothelial system [2; 4; 11]. In recent years, one of the leading areas in the diagnosis of cardiovascular diseases has become the study of molecular markers characterizing the functional state of the endothelial lining of blood vessels [3; 5].

It is important to identify predictors of microcirculation disorders and inflammationwith an assessment of operational characteristics [3]. At present, it can be stated that one of the main molecular markers of endothelial cell damage is monocyte chemoattractant protein-1 (MCP-1).

MCP-1 belongs to the class of chemokines, which are peptide molecules by their structure and have the properties of chemoattractants, the action of which is mediated by membrane receptors [6-8].

In addition to its function as a chemoattractant, which ensures the migration and extravasation of mononuclear cells into the site of inflammation, MCP-1 also acts as an inflammation mediator by activating resident cells.

The synthesis of MCP-1 is induced by IL-1β, α-TNF, γ-INF, IL-6, IL 4. Under the influence of MCP-1, proliferation of vascular smooth muscle cells also occurs with the secretion of proinflammatory cytokines [6-8].

Damage to cells by proinflammatory cytokines occurs through the formation of MCP-1 by activated monocytes and parenchymal cells, as a result of which the oxidation of free radicals is activated, which contributes to inflammation [7;9;10].

The direct relationship between the cytokine profile and microcirculation disorders in the pathogenesis of osteoarthritis has not been sufficiently studied. The sensitivity of endothelial cells and blood flow velocity are directly related to each other. This relationship is observed in most main arteries, which is manifested in the ability of endothelial cells to synthesize and secrete factors that promote relaxation or contraction of vascular smooth muscles. Endothelial cells have a high secretory capacity; based on this, it can be assumed that "endothelial tissue" is a unique endocrine organ that ensures homeostasis of the vascular walls [9-12].

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Purpose of the study

To characterize the functional state of the endothelium as the most important component of the microcirculatory bed and to identify the relationship between endothelial dysfunction (ED) and the inflammatory component, indicators of adaptation in female patients with OA.

Materials and methods of research

The study involved 78 female patients aged 50.5±0.58 years with a diagnosis of osteoarthritis. The patients were observed inThe patients were observed at the Multidisciplinary Clinic of the Tashkent Medical Academy in the Department of Rheumatology and SCAL Rheumatology and Arthrology.

The control group of 30 people (mean age 48±0.45 years) consisted of practically healthy women without characteristic signs of osteoarthritis.

During the experiment, the general clinical status of the patients was studied, an instrumental examination was carried out, and special laboratory methods were also used: counting the number of desquamated endothelial cells in the blood plasma using the Hladovec method.

By enzyme immunoassay method on the device StatFax assessed the functional state of the endothelium in the blood serum. Also determined were such indicators as the level of total nitric oxide, concentrations of VEGF, MCP-1 and C-reactive protein (CRP) in the blood serum.

Statistical processing of the obtained data was carried out using the computer programs Excel and STATISTICA 6.1.

In the statistical analysis, the Student's criterion (t) was used to determine the reliability of intergroup differences. For the correlation analysis, the Pearson correlation criterion® was used, which allows determining whether there is a linear relationship between changes in the values of various indicators (the relationship between indicators was perceived as weak - at $r < 0.3$, medium - at r from 0.3 to 0.7, strong at $r > 0.7$). The critical level of reliability of the null statistical hypothesis was taken to be 0.05.

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Research results and their discussion

The ED syndrome diagnosed in the examined patients with osteoarthritis is manifested by the following indicators: an increase in the amount of DEC, a decrease in NO, an increase in the concentration of VEGF (Table 1).

Table 1 Comparative analysis of the indices of the functional state of the endothelium in patients with OA and in the control group (M±□).

Indicators	OA patients (n=78)	Control group (n=30)	P
DEC, 104/l	10.14±6.86	3.02±1.21	<0.001
VEGF, pg/ml	366.8±256.1	158.86±72.83	<0.001
NO, µmol/l	9.14±1.25	29.43±3.34	<0.001

Note:p—reliability of differences in groups.

Also in the observation group, there is an imbalance of markers of endothelial dysfunction, leading to the predominance of vasospasm and disturbances at the level of the microcirculatory bed.

CRP was determined in 30 female patients with OA (mean age 43±0.49 years), and the average concentration of CRP in the blood was 52.24±33.58 mg/l. A significant increase in CRP in female patients with osteoarthritis (up to 52.24±33.58 mg/l) compared with the control group (p=0.03) was found in 47.6% of cases.

In patients with OA, the level of cytokine MCP-1, which is a chemotactic factor for immunocompetent cells, is increased in the blood serum compared to the control group in 91.7% of cases: 154.5±77.5 and 219.1±85.68 pg/ml, respectively, which indicates the presence of stimulation of the macrophage inflammatory response in osteoarthritis (Table 2).

Table 2 MCP-1 content in OA patients and in the control group (M±σ)

Indicators	Patients with osteoarthritis (n=25)	Control group (n=13)	R
MCP-1, pg/ml	219.1±85.68	154.5±77.5	0.029

Note:p—reliability of differences in groups.

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These results showed adequate possibilities for diagnosing endothelial dysfunction syndrome with a high degree of validity (Table 3).

Table 3 Tests Dot
Data on the functional state of the endothelium in a patient diagnosed with osteoarthritis

Tests Dot	Divisions	Diagnostic specificity, %	Diagnostic sensitivity, %	Diagnostic efficiency, %
DEC, 104/l	5	85.8	89.7	88.4
VEGF, pg/ml	80	79	89	80
NO, μmol/l	7	100	71.4	86.2

Cytokine (MCP-1) is specific for this pathology, since its diagnostic sensitivity was 83.4%, the diagnostic specificity of the test was 76%, and the efficiency was 75%.

Pathogenetic relationship between endothelial damage and neovasculogenesis processes has been established (r=+0.62). This relationship aggravates the microcirculation disorderin case of joint damage and causes progression of cartilage destruction, over the cartilaginous matrix. As a result of endothelial damage, there is a disruption in the production of the "circulation conductor" - nitric oxide. A decrease in the level of nitric oxide leads to the prevalence of vasospasm over vasodilation, which also aggravates the pathological process (r = - 0.56 between DEC and NO).

An inverse relationship was found between the neovasculogenesis marker and the vasodilation index (r= - 0.45). DThis relationship confirms that the microcirculatory link disorder is the most important element of pathogenesis. The relationship between VEGF and MCP-1 (r=0.424) proves that the progression of the inflammatory process in the cartilage, in the synovial membrane, above the cartilaginous part of the bone depends on the severity of the circulatory disorder at the microcirculation level.

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Conclusions.Based on the above, we can conclude that, based on correlation dependencies, a pathogenetic synergism of disturbances in microcirculation and in the cytokine profile has been established.

It was found that the discoordination of DE indicators worsens with the increase of the cytokine cascade, that is, the chronicity of the inflammatory process in osteoarthritis creates a favorable background for the conditions of vascular disorders syndrome.

In this case, the monocyte chemoattractant protein-1 is a direct preclinical predictor, since its concentration is increased even in the absence of synovitis.

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