

## 1. Introduction

Low back pain (LBP) is a significant medical and social problem. 80 % of people are likely to experience LBP throughout their lives, while 18 % of patients have almost constant ache in the lower back. The list of various causes of LBP (muscle, psychogenic, etc.) is headed by spinal osteochondrosis with its various neurologic manifestations. Moreover, the modern world witnesses a tendency in the increase of the number of young people who suffer from vertebral neurologic pain syndromes [1].

One of the most important reactions of the intervertebral disc and adjacent paravertebral tissues to the disc hernia is inflammation in the compressed part of the spinal motion segment. It is known that when the gelatinous nucleus is extruded and comes in contact with surrounding tissues it produces proinflammatory cytokines (primarily tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukins) contributing to the development of inflammation in the tissues surrounding the disc hernia [2].

Some clinical case studies [3] demonstrate that tissue samples obtained from surgical treatment of patients with hernia disc contain inflammation cells, mainly macrophages, that play an important role in the processes of the disc tissue resorption. In this regard, it has been a traditional practice to direct therapeutic efforts to blocking the biosynthesis of TNF- $\alpha$  and other proinflammatory cytokines to suppress inflammation.

Experimental studies performed on white New Zealand rabbits have produced evidence that blood vessels from the granulation tissue surrounding the herniated disc infiltrate the fibrous ring but do not penetrate the hyaline cartilage closure plate [4].

So, it has been established in today's numerous experimental and clinical studies that disc protrusion leads to a number of immunobiochemical processes and the inflammatory response of the body.

It has also been shown that despite the fact that the intervertebral disc is an avascular structure, the material of the disc extrusion often shows the presence of neovascularization, which is a part of the natural process of hernial reconstruction. Some researchers attribute the possibility of spontaneous resorption

## SOME MARKERS OF SYSTEMIC INFLAMMATORY RESPONSE AND ENDOTHELIAL DYSFUNCTION IN PATIENTS WITH NEUROLOGIC MANIFESTATIONS OF LUMBAR OSTEOCHONDROSIS

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**Abstract:** It has been established in numerous experimental and clinical studies that disc protrusion leads to a number of immunobiochemical processes and the inflammatory response of the body. It leads to a question: Aren't the processes of herniation accompanied with endothelial dysfunction which can develop in connection with the chronic inflammatory process? The following research goal is set to address these issues: to study blood plasma for the content of some chronic inflammation markers and endothelial damage such as fibronectin, tumor necrosis factor (TNF- $\alpha$ ) and soluble fms-like tyrosine kinase-1 (sFlt-1) in combination with the investigation of the functional state of the endothelium using Celermayer's test in males under the age of 45 without signs of obesity and somatic or vascular pathology with various neurologic manifestations of lumbar osteochondrosis.

85 male patients have been examined for neurologic manifestations of spinal osteochondrosis at the age from 19 to 45. The examined patients included 45 individuals with radiculopathy verified by neuroimaging and 40 individuals with reflex manifestations of lumbar osteochondrosis.

It has been shown that the examined patients of young age with exacerbation of discogenic radiculopathy accompanied with a prolonged pain syndrome experience an increase of fibronectin and tumor necrosis factor-alpha in plasma against the background of a decrease in the concentration of soluble fms-like tyrosine kinase-1 that are markers of inflammation and endothelial damage.

The obtained data imply that patients with neurologic manifestations of osteochondrosis need active preventive measures of cardiovascular diseases with the mandatory inclusion of endothelial-tropic therapy.

**Keywords:** Radiculopathy, lumbalgia, lumbar ischialgia, Celermayer's test, endothelium-dependent vasodilation, fibronectin, sFlt-1, TNF- $\alpha$ , endothelial dysfunction, systemic inflammatory response.

of the disc hernia to these processes [5].

All the above mentioned raises a question: Is there a systemic chronic inflammatory response in patients with a herniated intervertebral disc, and aren't the processes of herniation and subsequent spontaneous resorption of the intervertebral disc accompanied with endothelial dysfunction which can develop in connection with the chronic inflammatory process?

The following research goal is set to address these issues: to study blood plasma for the content of some chronic inflammation markers and endothelial damage such as fibronectin, tumor necrosis factor (TNF- $\alpha$ ) and soluble fms-like tyrosine kinase-1 (sFlt-1) in combination with the investigation of the functional state of the endothelium using Celermayer's sample in males under the age of 45 without signs of obesity and somatic or vascular pathology with various neurologic manifestations of lumbar osteochondrosis. The inclusion of only males into in the study group is dictated by the desire to limit the possible influence of complex cyclic processes in the female body on the laboratory parameters under study; the young age of patients is a guarantee of absence of systemic vascular diseases such as cerebral atherosclerosis and hypertension.

## 2. Methods

Throughout 2014–2017 at the clinic of nervous diseases of Bukovinian State Medical University of the city of Chernivtsi have been examined 85 male patients for neurologic manifestations of spinal osteochondrosis at the age from 19 to 45 (average age being 34.05 $\pm$ 5.7). The examined patients included 45 individuals with radiculopathy (20 of them

with S1 radiculopathy, 20 with L5 radiculopathy, 5 with L4 radiculopathy) verified by neuroimaging and 40 individuals with reflex manifestations of lumbar osteochondrosis (21 patients with lumbalgia and 19 patients with lumbar ischialgia).

Patient examination included: clinical somatic and neurologic examination in conjunction with the study of endothelium-dependent vasodilation of the brachial artery with the help of Celermayer's test [6].

The control group comprised 25 practically healthy individuals of the corresponding age and sex. Blood from an ulnar vein

was collected in the morning, on an empty stomach. The content of fibronectin, soluble fms-like tyrosine kinase-1 (sFlt-1), and tumor necrosis factor (TNF- $\alpha$ ) in plasma were determined by immunostimulatory ELISA technique according to the producer's procedure. The statistical processing of the results was performed using BioStat programme and Excel from Microsoft Office 2007 with the student's t-test definition. Differences between groups were considered statistically significant at  $p < 0.05$ .

**3. Results**

The average duration of the disease of all examined patients was  $6.3 \pm 0.4$  years. Patients complained of constant, severe pain in the lumbar spine. The intensity of the pain syndrome was measured with the help of a 10-point visual-analog scale of pain (VAS). The average indicator on the VAS scale was  $6.2 \pm 1.3$  for the study group.

90 % of all the analysed cases were connected with problems in the lowest two discs:  $L_v - S_1$  and  $L_{IV} - L_v$ , the rest 10 % were related to discs  $L_{III} - L_{IV}$ . Pronounced reflex and tonic manifestations along with signs of root dysfunctions make characteristic features of the clinical course of the detected root syndromes in the examined group of patients. The manual test discovered that 100 % of the examined patients had impairments in the muscular system. They included palpation induced muscle pain, increased muscle tone, hypotonic and hypotrophic changes in the muscles, zones of specific muscle compaction, active trigger points. In 85 % of cases paravertebral muscles, piriformis muscle, gluteal muscles and muscles of the anterolateral abdominal wall were affected.

Such muscular disorders indicate that young people develop myofascial pain syndromes in the setting of reflex muscular-tonic syndromes complicating their progress. The main role in their development is played by muscle strain in antiphysiological poses and wrong muscular stereotypes typical of modern young people who spend long hours at a computer both sitting at a table and lying on a couch with a notebook or a tablet.

The concentration of the studied endothelial dysfunction indices in plasma for the examined groups of patients is presented in **Table 1**. The obtained data have shown a probable increase in the levels of fibronectin and tumor necrosis factor-alpha against the background of a decrease in the concentration of soluble fms-like tyrosine kinase-1 in the group of patients with discogenic lumbar radiculopathy compared with the control group and the group of patients with reflex lumbalgia.

**Table 1**

Plasma levels of fibronectin, soluble fms-like tyrosine kinase-1 (sFlt-1) and tumor necrotic factor (TNF- $\alpha$ ) in patients with neurologic manifestations of lumbar osteochondrosis

Study groups	Fibronectin, g/l	sFlt - 1, ng/l	TNF- $\alpha$ , ng/l
Control (apparently healthy volunteers), n=25	0,3 $\pm$ 0,03	90,94 $\pm$ 0,56	3,8 $\pm$ 0,38
Patients with discogenic lumbar radiculopathy, n=45	0,47 $\pm$ 0,03 $p_1 < 0,005$	75,7 $\pm$ 3,79 $p_1 < 0,05$	7,47 $\pm$ 0,7 $p_1 < 0,05$
Patients with reflex lumbalgia, n=40	0,32 $\pm$ 0,04 $p_1 > 1$ $p_2 < 0,005$	92,27 $\pm$ 3,37 $p_1 > 0,99$ $p_2 < 0,001$	4,46 $\pm$ 0,67 $p_1 = 0,6$ $p_2 < 0,005$

Note:  $p_1$  – degree of probability of indicators difference compared with the control group;  $p_2$  – degree of probability of indicators difference between groups of patients; n – number of cases

**4. Discussion**

Now it is argued that angiogenesis is an important factor in the pathophysiology of many pathological processes. Today there is no doubt that there is a close interaction between synovial angiogenesis processes and inflammation in cases of rheumatoid arthritis and direct involvement of the immune system in these reactions [7]. The central role in these processes is played by the vascular endothelial growth factor (VEGF), one of the regulators of angiogenesis and immune inflammation. The immune system cells are VEGF producers themselves and they are both angiogenesis regulators and VEGF targets as they have specific receptors for interacting with this cytokine [8].

For performing virtually all their functions cells of the immune system directly contact the endothelium both on the way from the bloodstream to tissues and on the way from tissues to the lymphatic system; that is why VEGF can be considered as an important factor in physiological immunoregulation. VEGF can exert its influence not only locally in organs and tissues, but it can also have systemic impacts, moreover it has the ability to regulate the synthesis of cytokines and enhance the development of autoimmune inflammation [4].

The content of VEGF in serum and synovial fluid is significantly higher in patients with rheumatoid arthritis than in the group of virtually healthy donors who have low VEGF concentrations [3, 5].

The expression of VEGF is stimulated by a large number of pro-angiogenic factors, primarily by cytokines [8], among which the most notable is perhaps TNF- $\alpha$  whose concentration is significantly increased in the group of patients with discogenic lumbar radiculopathy compared to the control group and the group of patients with reflex lumbalgia.

An important role in the physiological response to the increased VEGF concentration is played by receptors on the surface of different cells. One of these receptors, which is located on the surface of vascular endothelial cells and macrophages, is type 1 VEGF receptor (Flt-1 – an enzyme similar to tyrosine kinase) [7].

Soluble fms-like tyrosine kinase-1 (sFlt-1) is a protein that is a splice variant of one of vascular endothelial growth factor receptors (VEGF) called Flt-1. sFlt-1 is a short form of Flt-1 receptor devoid of transmembrane and intracytoplasmic domains, which freely enters and circulates in blood (hence the name of this marker – soluble). sFlt-1 protein can bind and neutralize such angiogenic factors as VEGF. When VEGF is bound to sFlt-1 they become unable to interact with their receptors on endothelial cells and therefore lose their regular function. Thus, due to its function sFlt-1 belongs to antiangiogenic factors [5].

According to the research made by R. Pankov and K. M. Yamada (2002) the macrophage monocytic system of a human being in the conditions of latent endothelium damage tries to synthesize protective factors – glycoproteins, in particular fibronectin, which plays a significant role in the processes of adhesion, migration, growth and differentiation of cells [9]. It is the changes in the serum content of this opsonin that are an early sign of damage to intercellular interactions of endothelial cells. Fibronectin of blood plasma is antigenically identical to fibronectin on the surface of endothelial cells and has the property to break down under the influence of lipopolysaccharides of gram-negative bacteria walls, leukocyte proteases with heightened intensity of proteolytic enzymes activated in response to ischemic injury or inflammatory response, etc. [2].

The preliminary studies have demonstrated that patients with exacerbation of discogenic lumbo-sacral radiculopathy may experience a possible increase of such factors of endothelial

dysfunction as soluble vascular adhesion molecules (sVCAM – 1) and soluble E-selectin (sE-selectin) in blood plasma [10].

Thus, it can be assumed that there is a certain imbalance of angiogenic and antiangiogenic factors in such patients which requires further research that may be able to explain the mechanisms of spontaneous resorption of the intervertebral disc.

The mediatorial endothelial imbalance found in blood plasma of patients suffering from discogenic lumbar radiculopathy is confirmed by the violation of the endothelial function. Thus, as a result of the studies, it has been found that the indexes of endothelium-dependent vasodilatation of the brachial artery in the control group of patients is  $18,95 \pm 0,25$  %, which corresponds to the standard norm described in literature [6]. The group of patients with radicular syndromes has produced other indicators:  $11,72 \pm 0,3$  % (compared to the control,  $p < 0,01$ ).

Thus, young patients with normal body weight who suffer from chronic discogenic lumbar radiculopathy have signs of endothelial dysfunction expressed in the form of a decrease in the flow-dependent vasodilator response of the brachial artery in connection with an increase in the concentration of endothelial dysfunction markers and systemic inflammatory response.

In view of the revealed changes in the endothelial function it is promising to further investigate the endothelium function in order to clarify the development mechanisms of endothelial dysfunction accompanying neurologic manifestations of spinal osteochondrosis and to find ways of their optimal management. However, there is enough evidence in the obtained data at this stage of the research to claim that patients with neurologic manifestations of osteochondrosis need active preventive measures of cardiovascular diseases with the mandatory inclusion of *endothelial-tropic* therapy.

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