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Endothelin-1biomarker Features In Patients With Ankylosing Spondylitis After COVID-19

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Abstract

Currently, there is no doubt about the importance of the role of impaired endothelial functional state in the development of vascular pathology in a number of diseases, including rheumatic. With the advent and large-scale spread of a new coronavirus infection (COVID-19), a high rate of patient's hospitalizations with ankylosing spondyloarthritis (AS) and the development of extrapulmonary complications, such as myocardial injuries, kidney damage and vascular thromboembolism, were noted. The development of this phenomenon confirms the connection with pronounced endothelial dysfunction and its damage. This article presents the results of evaluation of endothelial dysfunction in AS patients undergoing COVID-19.

Keywords: ankylosing spondylitis, COVID-19, endothelial dysfunction.

Introduction

The coronavirus infection (COVID-19) caused by acute respiratory distress syndrome (SARS-CoV-2) has become a major challenge for patients with autoimmune rheumatic diseases. [2,3,7]. The high risk of complications, an increase in the number of hospitalizations and early incapacity in patients with AS and a previous coronavirus infection remain among the important problems that need to be solved. According to the references, the key for the development of most pathological processes in the body leads to endothelial dysfunction, which involves damage to endothelial cells and a mismatch between vasoconstriction and vasodilation. [1,6]. In autoimmune rheumatic diseases, including AS, immune complex inflammation comes to the fore in vascular damage, which is characterized by the development of productive lymphocytic vasculitis and activation of pro-inflammatory mediators, monocytes and T- cells, which lead to damage to the endothelium [5]. In recent years, data have appeared on damage to the endothelium and the violation of its vasoregulatory function in rheumatic diseases occurring with classic vasculitis of various organs, including AS [4,9]. In this article, we evaluated the severity of endothelial dysfunction in patients with ankylosing spondylitis who underwent COVID-19 by determining endothelin-1, as the main biomarker of endothelial dysfunction. The study of the severity of endothelial dysfunction and the development of methods for its correction in the future have as scientific as practical importance.

Materials and research methods. The study of patients was carried out prospectively on the basis of the rheumatology department at City Clinical Hospital of Tashkent. The study included 80 patients with a diagnosis of AS, according to the modified New York criteria (1984) and EULAR, of which 52 (86.67%) were men and 8 (13.33%) women. The average age of the patients was 39 ± 1.1 years, and the duration of the disease was 12.5 ± 0.9 years. Patients with obesity, hypertension, diabetes mellitus, cardiovascular and renal diseases were excluded from the study. In turn, the patients were divided into 2 groups: main and control. The main group included 40 patients with ankylosing spondylitis who underwent COVID-19. The 3rd disease activity prevailed (72%). The duration of the post-COVID period was 18±0.9 months. The control group included 40 patients with ankylosing spondylitis who did not have a history of COVID-19. The 2nd degree of activity prevailed (86%).

Mobility of the spine and hip joints was calculated according to the BASMI index,

disease activity and functional status in patients with AS - according to the BASDAI and BASFI indices, the number of affected enthesis - according to the MASES index, the type of joint damage (central, peripheral) was taken into account. ESR and C-reactive protein were also determined. All patients underwent a radiology examination of the spine and hip joints, a blood test for HLA-B27. The level of antibodies of the IgG class for SARS-CoV-2 (qualitative) was determined in all patients by ELISA. To determine the level of endothelin-1, the blood serum of all patients was taken and analyzed using «ELISA kit for Endothelin-1» reagents by ELISA. To estimate the vasoregulatory function of vessels reactive hyperemia test (as an endothelium-dependent stimulus) and nitrotroglycerin (NTG) in dosage 0.05 mg depended test (as an endothelium-independent vasodilator) were carried. To obtain an image of the right brachial artery (BA), measure its diameter and blood flow rate, the ACUSON 128 XP/10 ultrasound system was used.

The patient database was compiled using Microsoft Office Excel and statistical analysis was performed using MedCalc and Epi Info 2000.Statistical processing of the obtained results was carried out using packages of statistical programs "Microsoft Excel" using simple statistics, t - Student's criterion, correlation analysis, Pearson's frequency criteria (x^2). The difference between the studied parameters were recognized as reliable at $p < 0.05$.

Results. According to the obtained results, there were no significant differences due to sex and age among patients of both groups. The duration of ankylosing spondylitis in both groups was 13.6±8.1 years and 14.4±7.2 years, respectively. A comparative analysis of the results of both groups showed high indices of BASDAI, BASMI, BASFI and MASES in the main group rather than control one (Figure 1,2).

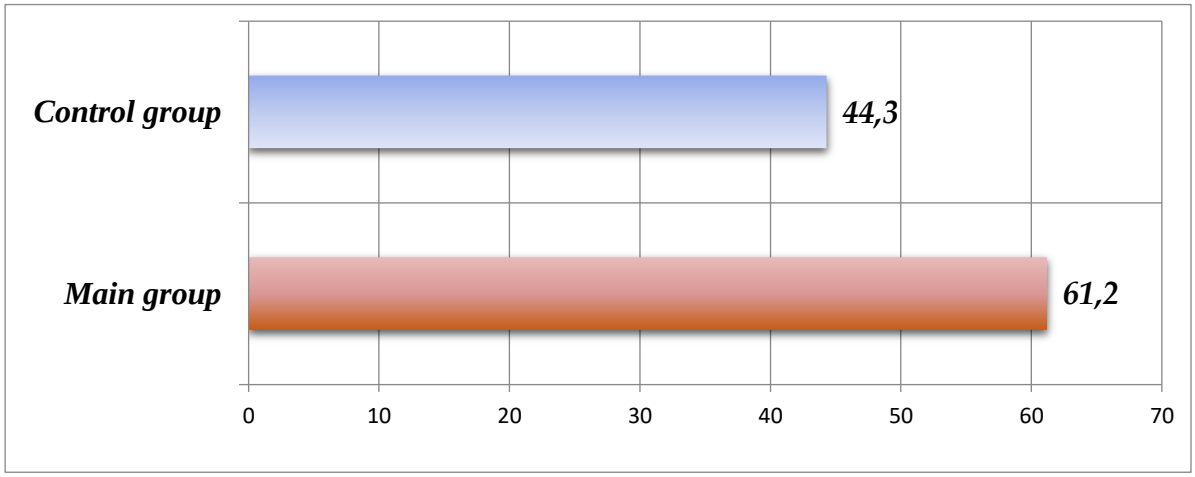

Figure 1. Mobility of the spine and hip joints according to the BASMI index

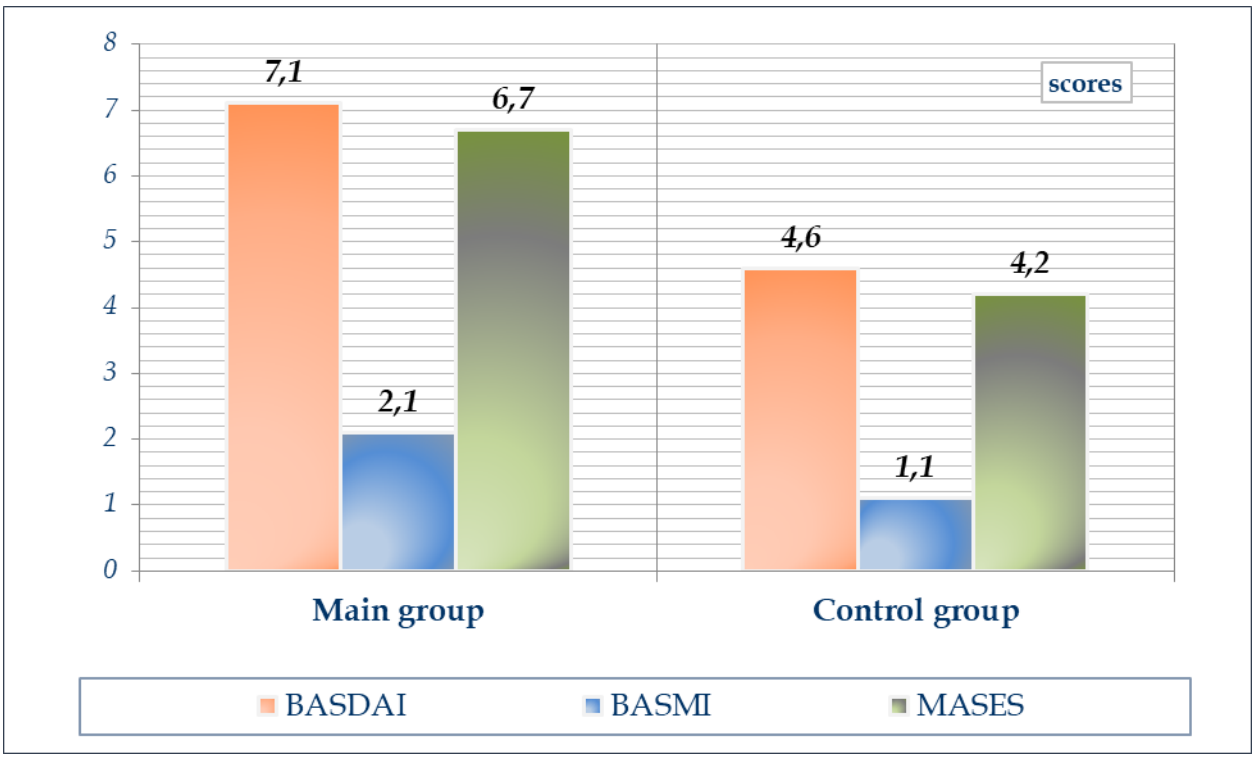

Figure 2. Disease activity and functional status in patients with AS - according to the BASDAI and BASFI indices, as well as the assessment of enthesitis according to the MASES index

ESR and C-reactive protein in patients with AS who underwent COVID-19 were 45.47±9.88 mm/h and 10.88±3.71 mg/l, which is 2 times higher than in the control group (16.18±5.65 mm/h and 5.56±1.54 mg/l, respectively) (Table 1). Fibrinogen levels remained within normal limits in both groups, however, this does not exclude the presence of coagulopathy in this category of patients.

Table 1. Comparative review of patient's with AS who underwent COVID-19

Data	**Main group(n=40)**	**Control group (n=40)**	**p**
Age(years)	38,3±11,6	36,9±8,4	>0,05
Women/men	11/29	16/24	<0,05
Disease duration	13.6±8,1	14.4±7,2	>0,05
C- reactive protein (mg/l)	10.88±3,71	5.56±1,54	<0,001
ESR (mm/h)	45.47±9,88	16.18±5,65	<0,001
Fibrinogen(g/l)	4.82±0,76	3.24±0,32	>0,05

The results of the study of endothelin-1 in the blood serum showed high levels in the main group - 247.8±14.6 pg/ml (p<0.05), while in the control group it was twice lower and was 128.3±18.3 pg/ml (p<0.001) (Fig.3). High values of endothelin-1 in patients of the main group indicate a pronounced endothelial dysfunction in patients with AS against the

background of a coronavirus infection. Endothelin-1 parameters weakly correlated with the level of C-reactive protein and ESR (r=0.55, P=0.00; r=0.32, P=0.04, respectively). Thus, the results of statistical analysis indicate significant differences between the datas.

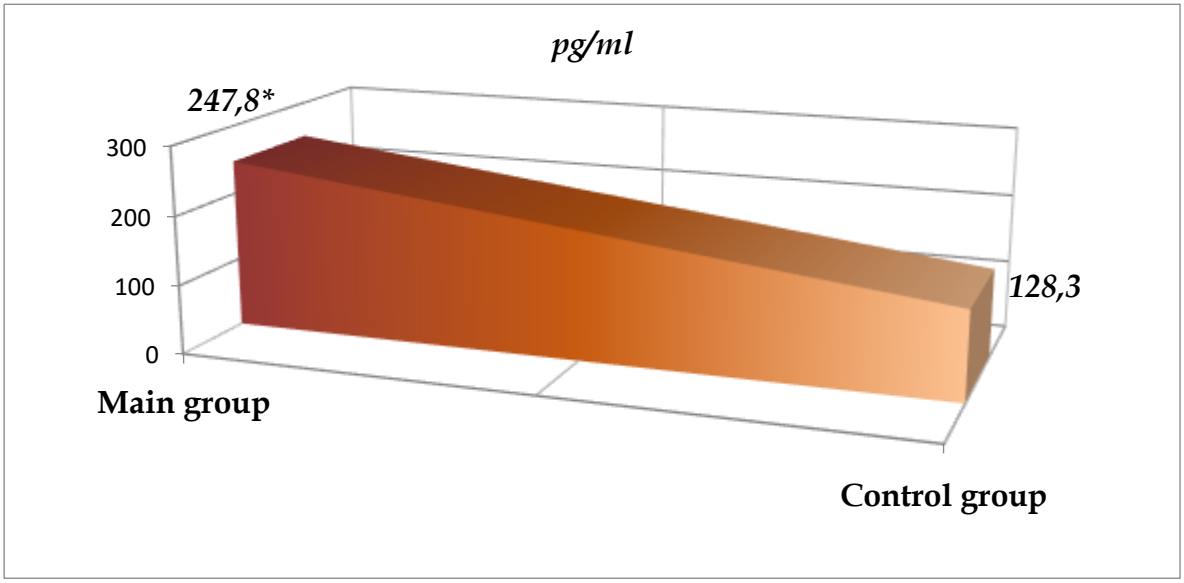

Figure 3. Values of endothelin-1 in patients of the main and control groups.

Table 2. Parameters of examination of the brachial artery in patients with ankylosing spondylitis

Data	Control group(n=40)	Main group (n= 40)
Initial blood flow velocity(m/s)	**0,8±0,034**	**0,62±0,17**
Initial diameter of BA, mm	**3,47±0,03**	**3,82+0,12***
Flow-mediated dilatation in 30 sec, %	**10,73+0,9**	**9,6±0,7**
Flow-mediated dilatation in 60 sec, %	**13,52±0,85**	**10,09+0,8****
NTG- induced vasodilatation, %	**16,35+0,76**	**22,48+1,22*****
Reactive hyperemia, flow increase, %	**151,74+3,09**	**142,92+4,19**

Note: Reliability of differences with control group: * - $p < 0.05$ * * - $p < 0.01$ * * * - $p < 0.001$

The examination of vasoregulatory function of endothelium in patients with ankylosing spondylitis showed wider diameter of BA in patients of control group ($p < 0.05$) compared to the diameter inpatients of main group (Table 2). The examined patients showed lower levels of flow-mediated dilation at the 60th second ($p < 0.01$) in patients with AS, underwent COVID-19, compared to similar indicators in patients of control group. According to the literature, flow-induced dilation is inversely proportional to diameter of vessels, and in arteries with a diameter of 6 mm or less, the average dilatation of the vessel is 10%. The lesser value or vasoconstriction are considered pathological [9]. In patients of main group the flow-dependent dilation did not exceed 10%, which was significantly more common than in patients in control group ($x^2 = 4.82$, $p < 0.05$). At the same time, the level of NTG-induced dilation in patients of main group was higher than in control ($p < 0.001$). In patients of control group, the levels of endothelium-dependent and endothelium-independent dilation differed slightly from each other in contrast to patients with AS underwent COVID-19 ($p < 0.001$).

In patients of control group, the flow-dependent dilation is 30 seconds less than the 60 ($p < 0.01$), that is, they have further dilation of the vessel within a minute. In patients with AS underwent COVID-19, it can be noted that the flow-mediated dilation for 60 seconds compared to 30 seconds increases by an average of 60% less than in the control group. Thus, in patients of main group, a decrease in flow-mediated vasodilation was established, which indicates a violation of the vasoregulatory activity of the endothelium.

Discussion.

The strongest vasoconstrictor, secluded in the body, is endothelin. Normally, endotelin-1 (ET-1) is synthesized only by stimulation of the endothelium by various factors, in particular adrenaline, thrombin, angiotensin, vasopressin. Endothelin regulates two opposite vascular responses (contraction and relaxation) by acting on different receptors. When exposed to ETA receptors located on vascular muscle cells, vascular contraction occurs. At the same time, activation of ETV receptors of the endothelium stimulates the synthesis of NO [11]. The highest level of ET is observed in multifocal atherosclerosis, nonspecific aortoarteritis, obliterating thrombangiitis, i.e., in diseases occurring with endothelial damage. Numerous experimental and clinical studies have identified an increase in plasma ET-1 in ankylosing spondylitis. To date, it is believed that the determination of the level of ET and its predecessor in AS is a reliable screening test for the diagnosis, estimation of the risk of developing and prognosis of this disease.

During the work, a negative effect of the previous coronavirus infection on the vasoregulatory function of the endothelium was found. The most significant changes were noted in patients with ankylosing spondyloarthritis and previous COVID-19 and a high degree of disease activity. If only endothelium-dependent vasodilation was impaired in the control group, flow-dependent and NTG-induced vasodilation decreased in the main group. The previous coronavirus infection causes a stronger violation of flow-dependent vasodilation than NTG-induced dilation. At the same time, a decrease in endothelium-independent vasodilation was found in patients with a high degree of AS activity compared to patients with minimal pathological process activity. Among patients with systemic manifestations, there were more patients with vasoconstriction at the 60th second than in the articular AS group. So, a connection has been established between the state of vasoregulatory function of the vascular wall and the presence of a previous coronavirus infection, a high degree of activity and the duration of the disease. In this case, a violation of flow-dependent vasodilation occurs. First of all, this may be due to a violation of the endothelial reaction to the production of a vasodilator such as nitric oxide (NO).

The revealed decrease in endothelium-dependent vasodilation is the result of a decrease in endothelial sensitivity to vasodilators in RA patients or accelerated NO inactivation under the influence of free oxygen radicals, the level of which is increased in AS [18]. This is consistent with the literature, according to which a number of factors associated with impaired vasoregulatory endothelial function act against the background of previous coronavirus infection in AS: activation of lipid and cytokine chain peroxidation processes, increased activity of the renin-angiotensin-aldosterone system, presence of hyperhomocysteinemia and hyperviscosity syndrome in patients, which through shear stress has a significant effect on endotheliocytes, which through the receptor apparatus of these cells provokes endothelial activation with increased synthesis of vasodilators, especially NO [7,11]. Given the preservation of NTG-dependent vasodilation, it can be noted that the vascular wall responds adequately to exogenous N0. Therefore, it is the synthesis of endogenous NO that is disrupted. Thus, the revealed disorders in patients with AS indicate damage to the endothelium with a change in its functional state against the background of a previous coronavirus infection and with minimal activity of the pathological process. These disorders are aggravated by an increase in AS activity and the development of systemic manifestations, as well as by an increase in the duration of the process. It can be imagined that in the absence of adequate therapy and, therefore, while maintaining activity, favorable conditions are created for the development of cardiovascular disorders, in

the pathogenesis of which endothelial dysfunction plays an important role [5].

Our study suggests that the inflammation is one of the pathogenic mechanisms of endothelial impairment development [9]. Endothelium dysfunction is a dominator leading to the malfunction of systems in patient with. AS is an autoimmune rheumatic disease causing the damage of spinal column and joints involving patients of young age. Moreover, an extra-articular exertings of other systems such as the pneumonitis, nephrytis and myocarditis are being estimated. The evaluation endothelin-1 level and flow- associated dilatation is particularly preferable to estimate [12]. Although the average difference in BASDAI was below the MCID, these findings suggest that the COVID-19 pandemic may have had an impact on AS disease activity through increased stress and anxiety. However, one of the faced obstacles was the small size and limited statistical analyzes.

Conclusions.

There's an array of scientific works about autoimmune and rheumatic diseases among COVID-19 researchers have been reported. It's estimated that COVID-19 can also impact of existing rheumatic diseases. Patients with AS and coronavirus infection showed more pronounced clinic and functional manifestations Determination of the endothelin-1 level and flow-mediated vasodilatation in patients with AS confirmed the presence of endothelial dysfunction against the background of a high degree of disease activity and its severity in patients with AS undergoing COVID-19. There's a need of larger studies to identify rheumatologic manifestations in patients suffered COVID-19.

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