ISSN NO: 2770-2936
December 2024

Impaired Endothelial Dysfunction In Patients With Ankylosing Spondylitis After Covid-19

Madina B. Rakhimova
Tashkent Medical Academy

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.

In recent years, research in the inflammatory rheumatic diseases has revealed an increased risk of developing endothelial disfunction, which is thought to be (partly) related to inflammation [1]. This association is well described for diseases such as systemic lupus erythematosus, antiphospholipid syndrome and rheumatoid arthritis [2]. On the other hand, patients with ankylosing spondylitis (AS) are known to have an overall mortality of about 1.6–1.9 times that of the general population [3], and excess mortality from circulatory disease has been found to be increased [4]. The pandemic of COVID-19 has caused a problem for patients with rheumatic diseases, particularly with ankylosing spondylitis, increasing the rate of hospitalization and disability.

The presence of APF2 -vascular cells on endothelium and smooth muscle is the reason for the involvement of the cardiovascular system in systemic damage, which is noted in almost all patients with COVID-19. It is a known that endothelial dysfunction associated with the introduction of the virus into the cells. This is accompanied by endothelial damage and also perivascular inflammation, which increases endothelial damage. Recent progress in ultrasonographic techniques has made possible the early detection of functional state of endothelial dysfunction by measuring the blood flow in brachial artery [6]. Recently flow-mediated dilatation (FMD) in the brachial artery has been used to detect endothelial function and is widely accepted as a non-invasive technique [9]. The main advantage of FMD is that it can detect endothelial dysfunction, which is frequently an initiator of the atherosclerotic process [10]. The aim of this study was to evaluate the degree of endothelial dysfunction in AS patients by using FMD techniques and detecting the level of endothelin- 1 as a specific marker of endothelial dysfunction.

Materials and methods. The study of patients was carried out at the rheumatology department of the Tashkent clinical hospital. The study included 80 patients with a diagnosis of ankylosing spondylitis according to the modified New York criteria and EULAR. All patients were divided into 2 groups: I group included 40 patients with ankylosing spondylitis without postcovid period, II group included 40 patients with ankylosing spondylitis and postcovid period. Patients with obesity, hypertension, diabetes mellitus, cardiovascular and renal diseases were excluded from the study. The control group included 40 healthy people with no acute and chronic diseases in anamnesis.

Mobility of the spine and hip joints was calculated according to the BASMI index. Disease activity and functional status were established based on BASDAI and BASFI indices. The number of affected enthesis was calculated according to MASES index. The type of joint damage (central or peripheral) was taken into an account. ESR and C-reactive protein levels were also determined. All patients underwent a blood test for HLA-B27. A blood pressure cuff was put on the projection of brachial artery to evaluate the flow- mediated vasodilatation. An air was bumped in up to 30 mm Hg above the systolic blood pressure for 5 min. We measured the diameter of brachial artery every 5s for 2 min. To determine endothelial- independent vasodilatation nitroglycerin tablet was given in 0,0025 mg/min dosage for 3 min. The blood sera of all patients were taken and analyzed using ELISA kit for Endothelin-1 to investigate the level of endothelin-1. The

ISSN NO: 2770-2936
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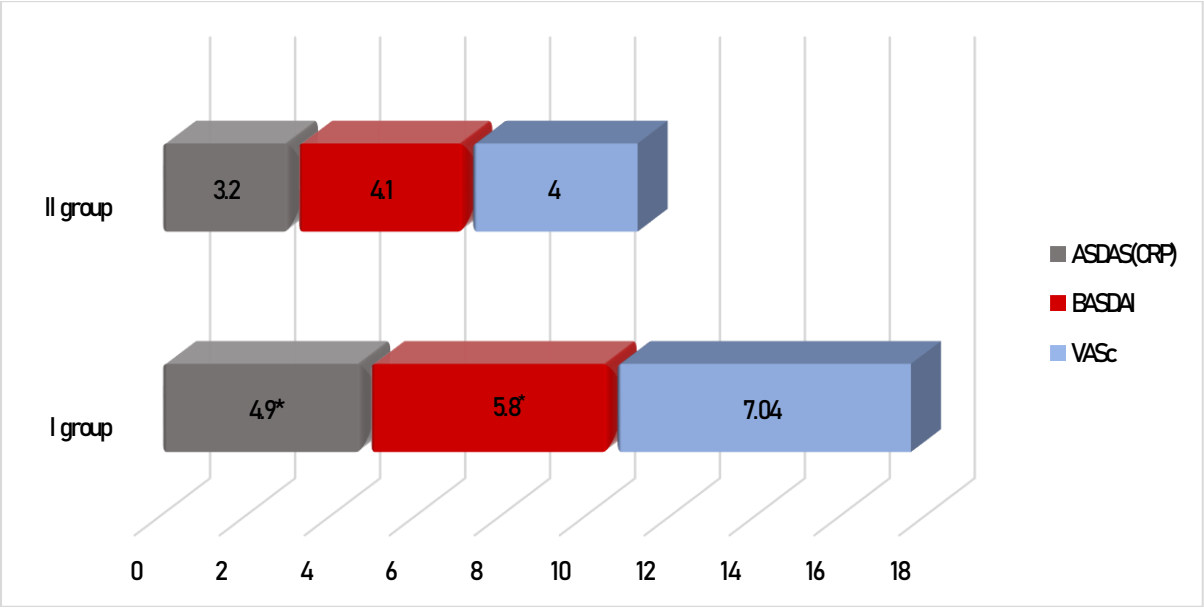
ACUSON 128 XP/10 ultrasound system was used to obtain an image of the right brachial artery, and to measure its diameter and blood flow rate.
Statistical analyzes were calculated on Otigin Pro 7 and Microsoft Excel programs. Spearman's correlation test was used to determine the association between endothelial vasodilatation and clinical parameters for AS.

Results and discussions.
Disease activity in the study groups was assessed by VAS, BASDAI, and ASDASRB. Thus, the high activity of the disease according to VAS was established in patients of group I who underwent COVID-19 (7.04 ± 1.08) and was 1.5 higher compared to the indicators of group II (4,0±0,81). BASDAI and ASDAS (CRP) showed very high disease activity in patients of group I (5,8±0,32 and 4,9± 0.45) and high activity in group II (4,1±0,621 and 3,2±0,61) (Fig.1). A comparative analysis of BASDAI indices in group I and group II showed that the highest scores were in group I patients when assessing the severity of neck, back, and joint pain (6,7±0,43), the level of joint pain during the week (7,1±0,47), and the duration of morning stiffness (6,2±0,66) compared to group II (4,2±0,44, 4.1 ±0,71, and 4.5 ±0,32, respectively).



* - validity of differences between the two groups $p < 0.05$

Figure 1. ASDAS(CRP), BASDAI, and VASc indices in I and II group patients
The endothelin-1 level was significantly higher in group I compared to group II (318.6 ±47,11 pg/mL versus 202,7±37,09 pg/mL, respectively, $p < 0.05$), while in group II the endothelin level was 5 times higher than the control group ($p < 0.01$). (Fig.1).The data obtained by us indicate a pronounced endothelial dysfunction in patients in the post-covid period.

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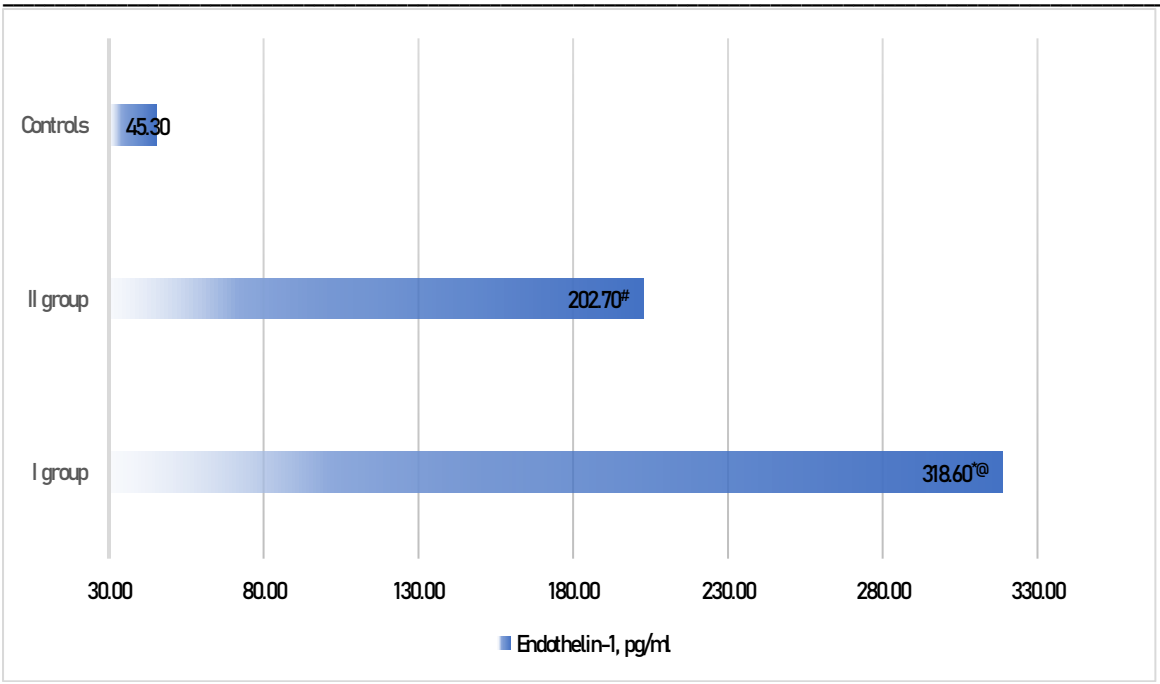

Note: Significant difference * -between groups I and II; # -between groups II and control; @ - between groups I and control

Figure 2. Endothelin-1 level in the study groups

As described above, the functional state of the endothelium has been studied in various chronic diseases: diabetes mellitus, nephropathy, hypertension and others. However, data in relation to ankylosing spondyloarthritis are scarce and inconsistent. Taking this into account, we examined the degree of flow-dependent vasodilation in the brachial artery in order to assess endothelial function in the study groups (Table 1.).

Table 1
Ultrasound Doppler results of the brachial artery in the study groups

Indices	I group	II group	Controls
Baseline blood flow velocity, m/s	0,56±0,09*	0,67±0,13	0,87±0,09
Initial BA diameter, mm	3,68±0,27	3,71±0,15	3,81±0,05
FMD on 60 sec, %	7,74±0,82*	9,87±1,47#	14,37±1,23
FMD on 120 sec, %	10,3±1,18*	13,6±0,87#	18,38±1,44
EIVD on 60 sec, %	14,21±1,47*	18,4±2,11	20,7±2,73
EIVD on 120 sec, %	17,6±1,18*	20,3±2,71#	24,1±2,19

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PI	3,19±0,7*	2,4±0,14	1,8±0,23
RI	0,96±0,4*	0,87±0,23	0,74±0,36

Note: * - significant differences between I and control groups, $p < 0.01$; # - significant differences between II and control group, $p < 0.05$

According to the results of the endothelial functional assessment, the examination of the initial diameter of the brachial artery showed no significant differences in the three study groups ($p > 0.05$). According to data from foreign studies, flow-mediated brachial artery dilation is directly proportional to the diameter of the artery, which means that in a vessel of 7 mm or less, the increase in the diameter of PA at each minute of dilation should be at least 10%. In the I group of patients, lower flow-dependent dilation (FMD) results were obtained compared to the II and control groups, namely, brachial artery dilation at 60 seconds in the I and II groups was below 10%, which confirms the presence of endothelial dysfunction in this category of patients ($p < 0.05$).

Comparing the FMD results at 60 seconds (1st minute dilation) between I and II groups, significant differences in parameters were obtained ($p = 0.03$), FMD of group I was lower than in II group on 120 seconds (2nd minute dilation),that is, at 120 seconds of dilation, the increase was below 10% (10,3±1,18 and 13,6±0,87, respectively). FMD results at 60 and 120 seconds in the control groups were 14,37±1,23 and 18,38±1,44%, respectively. It should be noted that in patients with AS who have undergone COVID-19, FMD on 60 seconds increases 61% less than in the control group, and on 120 seconds - by 56% less than in the control group. FMD at 60 and 120 seconds in the control group differed significantly from each other, indicating further vasodilation in subsequent minutes.

Thus, the results indicate a pronounced violation of the vasoregulatory function of the endothelium in patients in the postcovid period. This condition, according to literary sources, is justified by generalized endotheliopathy and the development of coagulopathy with perivascular inflammation.

The next step was the study of endothelium-independent peripheral vasodilation (EIVD) by testing with nitroglycerin (0.05 mg). 5 minutes after the administration of nitroglycerin, sublingual studies were conducted on the dynamics of the diameter of the brachial artery at 60 and 120 seconds after decompression. Thus, at 60 seconds, group I EIVD was reduced and significantly different from group II ($p < 0.05$). EIVD parameters of group II did not differ significantly from the control parameters, which showed an increase in the PA diameter of more than 10% at the 60th second of decompression. However, at the 120th second of decompression, a lower EIVD was observed in patients of group I, as opposed to the expected one, and amounted to 17,6±1,18%, while in group II the EIVD was 20,3±2,71%, which indicates PA dilatation less than 10%.

A pulse index (PI) study reflecting the vascular wall resistance index of the test vessel, which in group I showed high 3,19±0,7 values and was significantly increased in contrast to indicators II and control groups. The PI values in group II did not differ significantly from the control values and were close to the normal values.

The evaluation of the resistance index in the study groups, reflecting the difference between systolic and diastolic rates of vascular blood flow, showed significantly high values in group I compared to group II ($p = 0.03$). High RI (0,96±0,4) values in patients of group I indicate severe damage to the vascular wall AS due to risk factors, impaired systemic hemodynamics and association with cardiovascular events.

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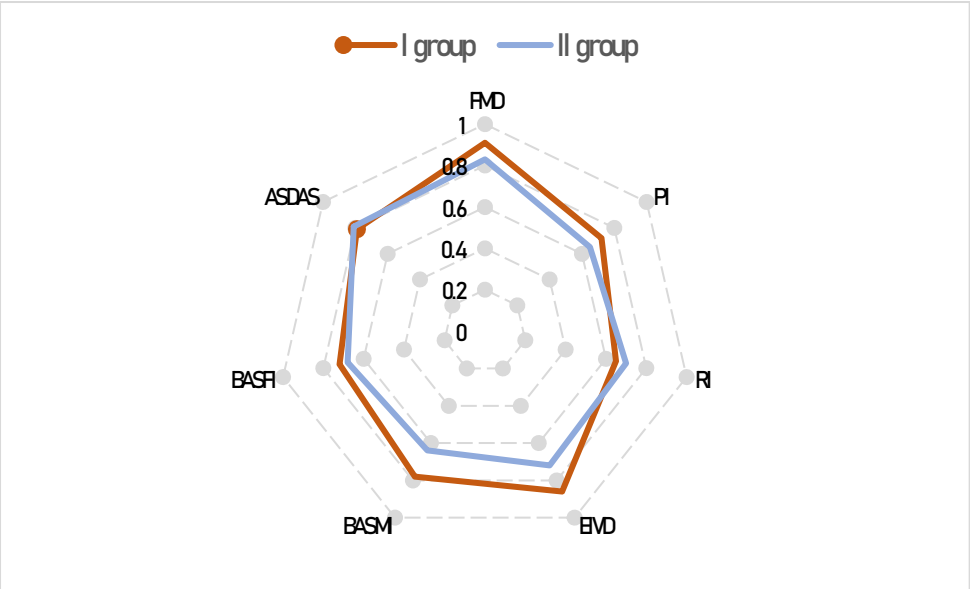

Figure 3. Correlation analyses between endothelin-1 and ultrasosnographic and activity indices

Conclusion.

AS is a chronic inflammatory rheumatic disease of the spine that affects between 0.2 and 0.9% of the population [21]. There are several characteristic extra-articular manifestations involving organs such as the eye, gastrointestinal system, kidneys, lungs and heart [3]. Clinically, it is relatively easy to measure endothelial function by using the capacity of the endothelium to elicit vasodilatation. Most investigations have used FMD in the brachial artery as an index of endothelial function [9].

Currently, there are a number of markers responsible for endothelial function: ADMA, endothelin-1, VEGF, ICAM-1, VCAM-1, and others [129; pp.55-67]. Considering the high sensitivity of the endothelium to certain injuries, a violation of the production of certain markers contributes to endothelial damage. Endothelin-1 is a highly sensitive peptide that is a powerful vasoconstrictor. Under the influence of factors such as hypoxia, ischemia, mechanical, as well as inflammatory mediators (IL-1,-6, TNF-α), its production is stimulated. In the work of Marder W. et al. the relationship of endothelin-1 and indicators of endothelium-dependent vasodilation with the pro-inflammatory cytokine IL-17 in patients with rheumatoid arthritis has been proven [12]. In our work, a study of endothelin-1 in 100 patients with AS showed significantly high values in patients of the main group, while high numbers were observed in patients with high and very high disease activity. Multivariate mathematical analysis of the relationship between endothelin-1 and BASDAI and ASDAS activity indices, functional activity of BASMI, VAS, morning stiffness and C-reactive protein showed a strong correlation in the main group of patients, which indicated that the severity of inflammation was proportional to endothelial damage.

The study of the functional state of the endothelium with a test of reactive hyperemia showed a decrease in the diameter of the brachial artery from the proper value at 60 and 120 seconds after decompression, as well as an increase in max systolic and a decrease in max diastolic blood flow in the main group. At the same time, these changes showed a high pulse index in the main group, which indicates a violation of the resistance of the vascular wall against the background of endothelial dysfunction.

Our study revealed that the endothelial function of AS patients who had undergone COVID-19 compared with healthy controls. No significant correlation was found between the FMD measurements and parameters such as sex, age, serum lipids, smoking habits, CRP level and disease activity scores; for some of these variables this may have been because of the small number of subjects included in the study. Thus, lack of correlation between FMD and disease activity scores needs to be confirmed by further studies with larger numbers of subjects.

The most significant limitation of this study is the small sample size and limited statistical power. Therefore, a larger study is needed to confirm our findings. Another limitation is that intraobserver variation was not assessed in this study.

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Despite these limitations, this study demonstrates impairment of endothelial function in AS. Further research should clarify the mechanisms involved and the clinical significance of this finding.

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