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CHARACTERISTICS OF ENDOTHELIAL DYSFUNCTION IN PATIENTS WITH ATOPIC DERMATITIS

Introduction. Skin lesions in atopic dermatitis (AD) are apparently associated with vascular changes, as blood vessels provide pathways for the transport of immune cells. The aim of the study: study of the state of endothelial dysfunction in patients with atopic dermatitis.

Materials and methods. 70 patients with AD were examined. Groups were formed depending on the SCORAD index (I subgroup – with SCORAD index up to 20 points, II – with SCORAD index 20-40 points, III subgroup – with SCORAD index from 40 and above points). Indicators of endothelial dysfunction of VEGF and VCAM-1 in blood serum were determined by the immunoenzymatic method.

Research results and their discussion. A significant percentage of deviations from the reference interval of both the level of VEGF (52 (74.3%) examined) and VCAM-1 (32 (45.7%) examined) in blood serum among AD patients was established. There were 4.6 times more people of the III subgroup with an elevated level of VEGF in blood serum than patients with a reference value ($p<0.001$) and 1.52 times more than among patients of the I subgroup ($p=0.0121$). Among the patients of the I, only the reference values of the vascular cell adhesion molecule-1 were found. Among individuals of the III subgroup with an elevated level of VCAM-1 was 1.9 times more than with its reference value ($p=0.016$). It was established that the level of VEGF in blood serum in patients of the III was 1.4 times higher compared to the level in patients of the II and 1.68 times higher than in patients of the I. Similar changes were found in the level of VCAM-1 in blood serum in AD patients. The highest level of VCAM-1 was found in patients of the III subgroup, which was 2.2 times higher than that in the II and 5.4 times in the I subgroups. In patients with AD with a minimum duration of the disease (1 year), the level of VEGF in blood serum was within the reference values. Probably the highest value of this indicator was noted in patients with a long course of the disease (16 and more years), ($p<0.05$).

Conclusions. A feature of atopic dermatitis is the development of endothelial dysfunction, namely due to an increase in the level of endothelial vasoactive factors VEGF, VCAM-1 ($p<0.01$). Violation of endothelial function in AD correlates with the severity of the disease ($p<0.05$). The increase in VEGF content is associated with the duration of AD ($p<0.05$).

Key words: vascular endothelial growth factor, vascular cell adhesion molecule1, atopic dermatitis.

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Особливості ендотеліальної дисфункції у хворих на атопічний дерматит

Вступ. Ураження шкіри при атопічному дерматиті (АД), очевидно, пов'язане із судинними змінами, оскільки кровоносні судини забезпечують шляхи транспортування імунних клітин. **Мета дослідження:** вивчення стану ендотеліальної дисфункції у хворих на атопічний дерматит. **Матеріали та методи.** Обстежено 70 хворих на АД. Були сформовані групи залежно від індексу SCORAD (I підгрупа – із індексом SCORAD до 20 балів, II – із індексом SCORAD 20-40 балів, III підгрупа – із індексом SCORAD від 40 і вище балів). Визначали показники ендотеліальної дисфункції VEGF та VCAM-1 у сироватці крові імуноферментним методом.

Результати досліджень та їх обговорення. Встановлено значний відсоток відхилень від референтного інтервалу як рівня VEGF (52 (74,3%) обстежених), так і VCAM-1 (32 (45,7%) обстежених) у сироватці крові серед хворих на АД. Значення VEGF та VCAM-1 залежали від підгрупи дослідження. Осіб III підгрупи із підвищеним рівнем VEGF у сироватці крові було в 4,6 рази більше, ніж хворих із референтним значенням (p<0,001) та в 1,52 рази більше, ніж серед хворих I підгрупи (p=0,0121). Серед хворих I підгрупи було виявлено лише референтні значення судинної молекули клітинної адгезії-1. Серед осіб III підгрупи хворих із підвищеним рівнем VCAM-1 було в 1,9 рази більше, ніж із референтним його значенням, (p=0,016). Встановлено, що рівень VEGF у сироватці крові у осіб III підгрупи був у 1,4 рази вищим у порівнянні із рівнем у хворих II підгрупи та в 1,68 рази – із хворими I підгрупи. Аналогічні зміни були виявлені і рівня VCAM-1 у сироватці крові у хворих на АД. Найвищий рівень VCAM-1 був виявлений у хворих III підгрупи, який у 2,2 рази перевищував такий у осіб II та у 5,4 разів у осіб I підгруп. У хворих на АД із мінімальною тривалістю захворювання (1рік), рівень VEGF у сироватці крові був у межах референтних значень. Вірогідно найбільше значення даного показника було відмічено у хворих при тривалому перебігу захворювання (16 та більше років), (p<0,05).

Висновки. Для атопічного дерматиту особливістю є розвиток ендотеліальної дисфункції, а саме за рахунок підвищенням рівня ендотеліальних вазоактивних факторів VEGF, VCAM-1 (p<0,01). Порушення ендотеліальної функції при АД корелює із тяжкістю захворювання (p<0,05). Підвищення вмісту VEGF повязане із тривалістю АД (p<0,05).

Ключові слова: фактор росту ендотелію судин, васкулярна молекула клітинної адгезії-1, атопічний дерматит.

Introduction. Skin lesions in atopic dermatitis (AD) appear to be associated with vascular changes, as blood vessels provide pathways for immune cell transport. Thus, eosinophils and lymphocytes play an important role among angiogenic factors. A crucial interplay between selectins, integrins, cytokines, chemokines, and various growth factors promotes angiogenesis, which leads to the exacerbation of AD. An increase in the adhesiveness of the endothelium and uncontrolled leukocyte adhesion are also of great importance in the pathogenesis of inflammation in AD [1, p. 4639].

It is known that specific surface molecules belonging to adhesive integrins provide close membrane interaction of blood leukocytes between themselves and the endothelium of capillaries, which is a necessary condition for cell migration in case of skin damage. The number of adhesive molecules on the surface of activated structures in AD significantly increases. The conducted studies revealed increased expression of intercellular adhesion molecules (ICAM-1 or CD54) on cells of eosinophils and neutrophils that migrate from the bloodstream or are in tissues, while increased expression of vascular-cellular adhesion molecules (VCAM-1) occurs on the membranes of the endothelium of capillaries) [2, p. 1471 – 1472].

Scientists have confirmed that the upregulation of adhesion molecules is mediated by the release of cytokines, such as interleukin-4, from cells found in atopic skin [3, p. 10661].

In addition, the value of oxidative stress, which is present in patients with atopy, has been proven in the occurrence of endothelial dysfunction [4, p. 1269; 5, p. 2136].

The angiogenic form of endothelial dysfunction is also associated with a violation of neoangiogenesis. The process of neoangiogenesis is a necessary factor for the maintenance of inflammation, preservation of erythema and edema in foci in AD. It is believed that VEGF is a characteristic mediator that helps increase vascular permeability in chronic dermatoses [6, p. 12035]. Some authors believe that changes in microcirculation during remodeling are associated with three mechanisms: angiogenesis, expansion of blood vessels, and increased permeability, and various mediators may participate in these processes [7, p. 783-784]. VEGF was previously known as a vascular permeability factor – the most specific proangiogenic cytokine, which plays a key role in the process of angiogenesis [8, p. 590-591]. It is also believed that VEGF plays a leading role in inflammation mediated by type 2 T-helpers and cytokine production [9, p. 5729].

Despite the fact that the problem of AD is sufficiently covered in the literature and national prevention and treatment programs have been developed, however, the pathogenetic basis of the disease remains the most complex and debatable.

The aim of our research was to study the state of endothelial dysfunction in patients with atopic dermatitis.

Methodology/Methods. The work was performed at the Department of Skin and Venereal Diseases with a course of postgraduate education of Vinnytsia National Medical University named after M. I. Pirogov from 2019 to 2022, on the basis of the Vinnytsia Regional Clinical Skin and Venereology Center of the Vinnytsia Regional Council. 70 patients with atopic dermatitis were included in the examination using clinical, immunoenzymatic, research methods. We formed groups based on the SCORAD index. The first subgroup consisted of 13 patients with a mild course of the disease (SORAD index up to 20 points), the second – 18 patients with a moderately severe course of AD (SORAD index up to 20-40 points), and the third subgroup – 39 patients with a severe course of the disease (SORAD index from 40 and above points).

All manipulations foreseen by the study design were initiated after providing information and signing informed consent by patients, control group persons, which were conducted in compliance with the ethical principles for human subjects, taking into account the basic provisions of GCP ICH and the Declaration of Helsinki of the World Medical Association on of biomedical research in which a person is the object (World Medical Association Declaration Of Helsinki 1964, 2000, 2008), the Council of Europe Convention on Human Rights and Biomedicine (2007) and the recommendations of the Committee on Bioethics under the Presidium of the National Academy of Sciences of Ukraine (2002).

Determination of indicators of endothelial dysfunction: VCAM-1 in blood serum was determined by the immunoenzymatic method using the "Human VCAM-1 ELISA Kit" (MyBioSource, USA, catalog no.: MBS3801534) in the research clinical and diagnostic laboratory of VNMU. named after M.I. Pirogov (certificate of the Ministry of Health of Ukraine on re-certification No. 049/15 dated March 2, 2015).

Human vascular endothelial growth factor (VEGF) in blood serum was determined by the immunoenzymatic method for quantitative determination in the SYNLAB laboratory (Kyiv).

Results and Discussion. During the study, a significant percentage of deviations from the reference interval of both the level of VEGF (52 (74.3%) examined) and VCAM-1 (32 (45.7%) examined) in blood serum among patients with atopic dermatitis was established. It should be noted that both VEGF and VCAM-1 values depended on the study subgroup (Table 5.1). Thus, there were 4.6 times more people of the III subgroup with an elevated level of VEGF in blood serum than patients with a reference value ($p<0.001$) and 1.52 times more than among patients of the I subgroup ($p=0.0121$). Among the examined patients of the II subgroup, there were also more patients with an increased level of VEGF in blood serum than with its reference value ($p=0.003$).

The results of the value of VCAM-1 in blood serum, depending on the subgroup of the study, are also noteworthy (Table 1). Thus, only the reference values of vascular cell adhesion molecule-1 were found among patients of subgroup I. Whereas, among persons of the III subgroup of patients with an elevated level of VCAM-1 was 1.9 times more than with its reference value ($p=0.016$) and 3 times more than among the examined subjects of the II subgroup ($p=0.001$). Among the patients of the II subgroup, almost the same number of patients with both the reference value of VCAM-1 and its elevated level in blood serum was found ($p=0.741$).

It is worth noting that patients with atopic dermatitis, regardless of the subgroup of the study, who had a significantly lower level of VEGF in blood serum compared to the indicator of the control group need more in-depth observation. Since, according to the literature, a low level of vascular endothelial growth factor in blood serum can predict AD persistence [10, p. 035002].

In the following, we analyzed the level of markers of endothelial dysfunction in blood serum of AD patients. It was established that the level of VEGF in blood serum in patients of subgroup III was 1.4 times higher compared to the level in patients of subgroup II and 1.68 times higher than in patients of subgroup I. It should also be noted that the level of VEGF in the blood serum of patients of III and II subgroups had a significant difference compared to the value of the indicator in the control group, $p<0.001$.

Similar changes were found in the level of VCAM-1 in blood serum among AD patients depending on the study subgroup. Thus, the highest level of the vascular cell adhesion molecule-1 was found in patients of the III subgroup, which was 2.2 times higher than in individuals of II and 5.4 times in individuals of I subgroups. The difference in the level of VCAM-1 in patients of the II subgroup was also significant in comparison with the level in patients of the I subgroup, $p<0.001$.

On the other hand, in patients of the I subgroup, both the level of VEGF and VCAM-1 in blood serum did not have a significant difference compared to the indicator in the control group, $p>0.05$.

The next step of the study was to analyze the correlation between indicators of endothelial dysfunction and the SCORAD index in the examined patients. Thus, we established a direct moderate correlation between vascular endothelial growth factor and the SCORAD index in patients of the III subgroup ($r=0.621$; $p=0.004$), II subgroup ($r=0.571$; $p=0.0032$) and a weak one in patients of the I subgroup ($r=0.339$; $p=0.042$).

Table 1

Frequency of deviations from the reference interval of the VEGF index among patients with atopic dermatitis (m, %, p, $\chi 2$)

Indicator	I subgroup (n=13)	II subgroup (n=18)	III subgroup (n= 39)	Control group
VEGF < 150 pg/ml	6 (46,15)	5 (27,78)***	7 (17,95)*,**	
VEGF > 150 pg/ml	7 (53,85)	13 (72,22)	32 (82,05)	
DI	0.97 (0.72, 1.37)	1.42 (1.16,1.38)	1.49 (1.31,1.8)	
χ^2	0.005	8.069	9.176	
P	0.867	0.003	<0.001	
VEGF (pg/ml) Me (Q1 – Q3)	164.13 (143,25-181.22)	197.68 ^^ (183,58-208,11)	276.10 ^ (212,11-341.28)	151.12 (116,13-155.21)
VCAM-1 <22,29 ± 2,51 ng/ml	13 (34.2)	10 (26.32)	15 (39.5)#	
VCAM-1 >22,29 ± 2,51 ng/ml	0	8 (25.0)	24 (75)	
DI	1.46 (1.17, 1.81)	1.23 (0.81, 1.72)	4.61 (1.24, 9.3)	
χ^2	18.17	0.931	5.539	
P	<0.001	0.741	0.016	
VCAM-1 (ng/ml) Me (Q1 – Q3)	26,04 (23,7-29,7)	65,46&& (34,1-254,1)	140,87& (38,5-487,1)	22,29 (19,5-24,4)

*Notes: * probable difference when comparing the VEGF indicator of III subgroup and I subgroup, p= 0.0121;*

*** probable difference when comparing the VEGF index of III subgroup and II subgroup, p=0.1153;*

**** probable difference when comparing the VEGF index of II subgroup and I subgroup, p=0.1241.*

 # Probable difference when comparing VCAM-1 indicator of III subgroup and II subgroup, p=0.001.

^ – probable difference when comparing the VEGF III subgroup with other subgroups and the control group, p<0.001;

^^ – probable difference when comparing the VEGF indicator of the II subgroup with the value of the I subgroup and the control group, p<0.05;

& – probable difference when comparing the VCAM-1 indicator of the III subgroup with other subgroups and the control group, p<0.001;

&& – a probable difference when comparing the VCAM-1 indicator of the II subgroup with the value of the I subgroup and the control group, p<0.001.

Instead, a weak positive correlation was found between VCAM-1 index and SCORAD index regardless of the severity of atopic dermatitis.

In a further study, we found comparisons of endothelial dysfunction in patients both at the beginning of AD and during the duration of the pathological process. Thus, in AD patients with a minimum duration of the disease (1 year), the level of VEGF in blood serum was the lowest. At the same time, probably the highest value of this indicator was noted in patients with a long course of the disease (16 and more years), ($p<0.05$).

On the other hand, the level of VCAM-1 in blood serum in patients with AD did not have a consistent dependence on the duration of the disease. However, the lowest level of VCAM-1 in blood serum was found in patients with a disease duration of 1 year, $p<0.05$.

The perspective of our further research will be to study the effect of vitamin D on markers of endothelial dysfunction. According to literature data, hydroxyvitamin D may influence VEGF expression [11, p. 108444].

Conclusions. For atopic dermatitis, the key feature is the development of endothelial dysfunction, namely due to an increase in the level of endothelial vasoactive factors VEGF, VCAM-1 ($p<0.01$).

At the same time, the violation of endothelial function in such patients correlates with the severity of the disease ($p<0.05$). In addition, an increase in the content of VEGF is associated with the duration of the disease ($p<0.05$).

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