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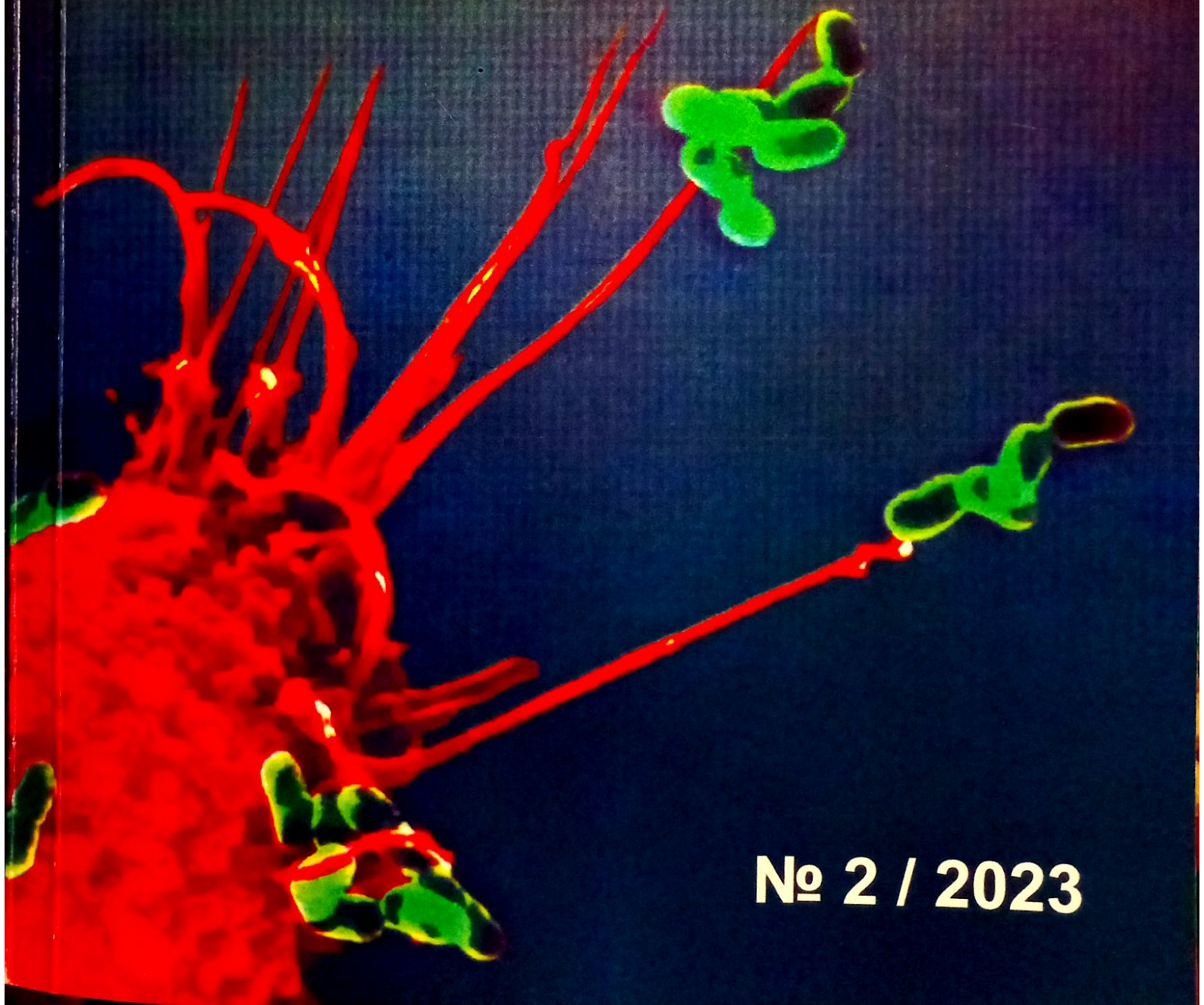

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A MODERN VIEW ON THE PROBLEM OF ENDOTHELIAL DYSFUNCTION IN PATIENTS WITH ANKYLOSING SPONDYLOARTHRITIS

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Annotation. Ankylosing s pondylitis (AS) or Bechterew's disease is a chronic systemic disease of the joints with predominant localization of the process in the sacroiliac joints, joints of the spine and paravertebral soft tissues. Over a five-year period, the incidence of the adult population of the Russian Federation increased by 32.2% for spondylopathies. The incidence of spondylopathies among inflammatory diseases of the joints ranks second after rheumatoid arthritis. The increase in incidence per 100,000 population is especially high in the Far East, North Caucasus, and Siberian federal districts (by 47.5%, 48.4%, and 39.7%, respectively) [1].

Patients with AS are at risk for the development of cardiovascular pathology. It is known that traditional risk factors (TRF) for cardiovascular diseases play an important role in the development of atherosclerotic process, which subsequently leads to stroke, myocardial infarction, unstable angina and other adverse complications. A number of modern studies have shown that even in the absence of TRF in patients with AS, mortality is 1.5 times higher than the population level, the main causes of death in this category are secondary amyloidosis and cardiovascular pathology [2].

Han C. et al. [3] found an increase in cardiovascular risk in patients with AS compared with the general population. In the studies of Peters M. et al. [4] proved that the presence of myocardial infarction in patients with AS is observed in 4.4% of cases, while in the general population comparable in age and sex, myocardial infarction was detected only in 1.2% of cases.

In this regard, the issue of identifying other risk factors for the development of severe cardiovascular pathology in patients with AS becomes relevant. If these risk factors are identified, it will be possible to preserve the quality of life of patients as long as possible. That is why, in the treatment of AS, the question of a personalized approach to the choice of therapy tactics is increasingly being raised, based on the variety of clinical manifestations of the disease, their severity, the presence of unfavorable prognosis factors, comorbid conditions, patient preferences and expectations [5].

Among the main possible causes, one can consider both the "accumulation" of classical cardiovascular risk factors due to exposure to systemic inflammation, genetic predisposition and/or adverse effects of drugs, as well as direct damage to the cardiovascular system of autoimmune origin. The combined negative impact of the above factors cannot be excluded [6].

It is known that the cause of the development of cardiovascular diseases in patients with AS is endothelial dysfunction, but the clinical and pathogenetic role of these changes is not well understood. At present, the involvement of endothelial dysfunctions both in the process of atherosclerotic plaque formation and its destabilization has been proven, which leads to plaque rupture, exposure of collagen, activation of the coagulation system, and thrombosis [7].

Among the causes that can initiate endothelial dysfunction, systemic inflammation and activation of lipid peroxidation processes should be highlighted. According to researchers, inflammatory mediators can cause activation and damage to the endothelium, leading to disruption of its function, which has been convincingly proven in articular pathology, in particular, in osteoarthritis [8].

The study and understanding of the causes of endothelial dysfunction (ED) in rheumatic diseases seems promising, as it will reveal the mechanisms of the rapidly progressive atherosclerotic process and high cardiovascular mortality. In rheumatological patients, the change in endothelial function is a unique "crossroads" of pathogenetic pathways, on the one hand, determining the progression of the immunoinflammatory process (traffic of immunocompetent cells to target organs, antigen-presenting function and production of cytokines by activated endothelial cells), on the other hand, leading to accelerated progression atherosclerosis and an increased risk of its complications (decrease in the antithrombogenic potential of the endothelial lining, subendothelial accumulation of oxidative low density lipoproteins, foam cells, and inflammatory cells) [9].

An analysis of literature data showed that the main causes of ED are the association of inflammatory markers (asymmetric dimethylarginine, homocysteine, endothelin 1-21, type 1 vascular endothelial adhesion molecule, type 1 intercellular adhesion molecule, reactive hyperemia index), impaired adsorption-rheological blood properties, as well as persistent systemic inflammation. It has now been revealed that asymmetric dimethylarginine (ADMA), which inhibits nitric oxide synthase, is the main marker of inflammation that contributes to the development of endothelial dysfunction. The main functions of nitric oxide in the cardiovascular system are associated with its vasodilatory effect, inhibition of smooth muscle cell proliferation, as well as platelet aggregation and adhesion [10]. That is why, with an increase in ADMA in the blood plasma, insufficient vascular vasodilation occurs, endothelial function worsens, which contributes to the development of cardiac pathology.

Ogawa T. et al. pathways of ADMA metabolism were studied [11]. When labeled ADMA was administered intravenously to rats, 2% of the molecules were excreted in exhaled carbon dioxide, 14% was excreted in the urine, and 86% accumulated in the liver, pancreas, and kidneys in the form of citrulline. In subsequent works by these authors, two enzymes involved in the hydrolysis of

ADMA were isolated. These enzymes were dimethylarginine dimethylaminohydrolase (DDAH) [12] and alanine glyoxylate aminotransferase 2 (AGAT2) [13]. DDAG is the main enzyme hydrolyzing about 80% of ADMA to form dimethylamine and citrulline. DDAG is divided into two main isoforms: DDAG1 and DDAG2 [14]. DDAG1 is synthesized in the digestive, respiratory, excretory systems, central nervous system, and male reproductive system. DDAG2 is synthesized in the bone marrow, digestive system, excretory system, and female reproductive system [15].

Authors Achan V. et al. conducted a study during which the synthesis of DDAG1 was increased in the body of transgenic mice, as a result, there was a decrease in the level of ADMA in blood plasma and tissues and an increase in the production of nitric oxide [16]. Increased expression of DDAG2 caused a similar effect in transgenic mice [17]. Thus, an increase in the activity of DDAG1 and DDAG2 may underlie the development of drugs that reduce the level of ADMA in blood plasma [18]. However, Kostourou V. et al. found that an increase in the level of ADMA promotes tumor growth [19]. AGAT2 is an enzyme providing an alternative pathway for ADMA metabolism. This enzyme is expressed in cells of the loop of Henle [20]. As a result of the hydrolysis of ADMA by AGAT2, α-keto-δ-(NG, NG-dimethylguanidino)valeric acid is first formed, which is subsequently converted to γ-(dimethylguanidino)butyric acid.

In the course of numerous studies, it has been found that there are a number of drugs that help reduce the level of ADMA in blood plasma. These drugs include angiotensin-converting enzyme inhibitors [21] and angiotensin receptor blockers [22]. However, the exact mechanism of the effect of these drugs on the level of ADMA in blood plasma is currently poorly understood [18].

A.L. Maslyansky et al., 2015, assessed the functional state of the endothelium in patients with rheumatological diseases [9]. The researchers studied the effect of various inflammatory markers on ED, as well as the increase in the level of ED markers depending on the nosological form. Based on a survey of 286 patients with rheumatological diseases, the researchers concluded that in patients with AS, the levels of such markers as type 1 intercellular adhesion molecule, type 1 vascular endothelial adhesion molecule, type 1, were increased, in addition, the greatest increase in homocysteine levels was noted in patients with AS. compared with other groups of rheumatic patients. At the same time, ADMA levels in AS were lower than in patients with systemic scleroderma, rheumatoid arthritis, and systemic lupus erythematosus, but higher than in the control group. There is also evidence that the well-known association of an increase in homocysteine with the development of cardiovascular diseases is mediated by mechanisms involving ADMA.

Homocysteine is considered an important risk factor for heart disease. Multiple data on an increase in homocysteine suggest that a decrease in total homocysteine concentration by 3 μmol/l can reduce the risk of coronary heart

disease by 16%, deep vein thrombosis by 25% and strokes by 24% [23]. To date, we can consider the association of high levels of homocysteine and endothelial dysfunction, stimulation of homocysteine production and secretion of cholesterol in liver cells, the relationship between homocysteine levels and thrombotic diseases, stimulation of proliferation of smooth muscle cells of the vascular wall and other pathological conditions that cause the development of atherosclerosis and disease with homocysteine to be considered proven. circulatory systems. Even specific levels of homocysteine are given, which should be taken into account during prevention: at a level of 14 μmol/l, primary prevention is recommended, at a level of 11 μmol/l and the presence of pathology, secondary prevention is recommended [24]. Recent studies have shown that the effect of homocysteine on cardiovascular health is mediated by ADMA [25]. It has also been proven that a decrease in homocysteine levels with the use of folic acid is accompanied by a decrease in the manifestations of ED [26]. As a result of studies conducted by Adam Kemeny-Beke et al., 2011, from the University of Northern Iowa [27], it was found that serum ADMA levels were significantly increased in patients with AS compared with patients with osteoarthritis (0.95 ± 0 .17 μmol/l vs. 0.70±0.25 μmol/l, $p<0.001$), the researchers concluded that ADMA can serve as a marker of systemic inflammation in AS.

In general, data on the role of ADMA in the development of cardiovascular disorders in patients with AS are scarce. The authors of Gian Luca Erre et al., 2011, studied the plasma level of ADMA and its association with atherosclerotic diseases in AS [28]. Seventeen AS patients who did not suffer from cardiovascular diseases and 17 healthy control patients were selected for the study; The groups were comparable in terms of gender, age, and risk factors for atherosclerosis. Plasma ADMA levels were assessed by capillary electrophoresis. In patients with AS, plasma ADMA concentration was higher compared to the control group (0.65±0.10 μmol/l versus 0.54±0.07 μmol/l, $p = 0.001$).

Research results of E.D. Egudina et al., 2017, proved that in addition to inflammation markers, there are also other factors that contribute to the development of ED in patients with AS. According to the authors, ED develops in 53% of patients with AS and, in the presence of vascular pathology, is accompanied by an increase in the blood concentration of cGMP and a decrease in the content of prostacyclin [29].

In his work on the role of systemic inflammation and endothelial dysfunction in patients with AS, D.A. Poddubny et al., 2007, provided evidence that patients with AS have a significantly increased level of circulating endotheliocytes, which are a marker of endothelial damage, and an increased level of von Willebrand factor. In 47% of patients, endothelium-dependent vasodilation is reduced [30]. The study shows the relationship between systemic inflammation and endothelial dysfunction.

Thus, the analysis of literature data proves that, in addition to the TFR of developing cardiovascular diseases, patients with AS have additional risk factors associated with the activity of systemic inflammation and indicating damage and dysfunction of the endothelium. One of the informative indicators of endothelial dysfunction is an increase in the level of ADMA in blood plasma, which was detected in patients with AS in independent studies. An increase in ADMA levels prevents adequate vasodilation, which potentiates the development of cardiovascular diseases. At the moment, the question remains whether an increase in the level of ADMA is an etiological factor or just a biological marker of cardiac pathology. The role of ADMA in the development of damage to the heart and blood vessels, including in patients with AS, can be proven after the development of specific therapy aimed at reducing the level of ADMA. Follow-up monitoring of the development of cardiovascular disease in conditions of exclusion of the effect of elevated levels of ADMA on the endothelium will help in understanding the pathogenetic mechanisms of its development. Research in this area is of practical importance, as it creates prospects for the management of the pathological process and contributes to the development of preventive strategies.

LITERATURE

1. Balabanova R.M., Dubinina T.V., Erdes Sh.F. Dynamics of the incidence of rheumatic diseases in the adult population of Russia in 2010-2014. Scientific and practical rheumatology. 2016. 54(3). 266-270. DOI: 10.14412/1995-4484-2016-266-270.

2. Poddubny D.A., Rebrov A.P. Cardiovascular risk in patients with ankylosing spondylitis: the role of systemic inflammation and endothelial dysfunction. Regional Pharmacotherapy in Cardiology. 2008. 5. 71-76.

3. Han C., Robinson D.W. Jr., Hackett M.V. Paramore L.C., Fraeman K.H., Bala M.V. Cardiovascular disease and risk factors in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. J. Rheumatol. 2006. 33 (11). 2167-2172.

4. Peters M.J., Visman I., Nielen M.M., Dillen N.V., Verheij R.A., Horst-Bruinsma I.E., Dijkmans B.A., Nurmohamed M.T. Ankylosing spondylitis: a risk factor for myocardial infarction? Ann Rheum Dis. 2010. 69(3). 579-581. DOI:10.1136/ard.2009.110593

5. Erdes Sh.F. Basic principles of therapy for ankylosing spondylitis (Bekhterev's disease). Scientific and practical rheumatology. 2013. 51(6). 686-695. DOI: 10.14412/1995-4484-2013-686-95.

6. Rebrov A.P., Gaidukova I.Z., Poddubny D.A. Cardiovascular pathology in patients with ankylosing spondylitis. Scientific and practical rheumatology. 2012. 51(2). 100-105.

7. Polonetsky O.L., Polonetsky L.Z. Endothelial dysfunction and atherosclerosis. Medical news. 2012. 6. 6-11.

8. Alekseenko E.Yu., Govorin A.V. State of endothelial function in

patients with primary osteoarthritis. Siberian Medical Journal (Irkutsk). 2010. 8. 106-108.

9. Maslyansky A. L., Zvartau N. E., Kolesova E. P., Bezkishkiy E. N., Shevchuk I. A., Vasilyeva E. Yu., Mazurov V. I., Konradi A. O. Evaluation of the functional state of the endothelium in patients with rheumatological diseases. Arterial hypertension. 2015. 21(2). 168-180.

10. Manukhina E.B., Malyshev I.Yu. The role of nitric oxide in the development and prevention of endothelial dysfunction. Bulletin of VSMU. 2003. 2. 5-17.

11. Ogawa T., Kimoto M., Watanabe H., Sasaoka K. Metabolism of NG,NG-and NG,N'G-dimethylarginine in rats. Arch Biochem Biophys. 1987. 252. 526-537.

12. Ogawa T., Kimoto M., Sasaoka K. Purification and properties of a new enzyme, NG, NG-dimethylarginine dimethylaminohydrolase, from rat kidney. J Biol Chem. 1989. 264. 10205-10209.

13. Ogawa T., Kimoto M., and Sasaoka K. Dimethylarginine: pyruvate aminotransferase in rats. Purification, properties, and identity with alanine: glyoxylate aminotransferase 2. J. Biol. Chem. 1990. 265. 20938-20945.

14. Leiper J.M., Santa M., Chubb A., MacAllister R.J., Charles I.G., Whitley G.S., Vallance P. Identification of two human dimethylarginine dimethylaminohydrolases with distinct tissue distributions and homology with microbial arginine deiminases. Biochem J. 1999. 343. 209-214.

15. Tran C.T., Fox M.F., Vallance P., Leiper J.M. Chromosomal localization, gene structure, and expression pattern of DDAH1: comparison with DDAH2 and implications for evolutionary origins. Genomics. 2000. 68. 101-105.

16. Achan V., Dayoub H., Adimoolam S., Jacobi J., Stuehlinger M. C., Wang B. Y. Dimethylarginine dimethylaminohydrolase regulates nitric oxide synthesis: genetic and physiological evidence. circulation. 2003.108.3042-3047.

17. Hasegawa K., Wakino S., Tatematsu S., Yoshioka K., Homma K., Sugano N., Kimoto M., Hayashi K., Itoh H. Role of asymmetric dimethylarginine in vascular injury in transgenic mice overexpressing dimethylarginie dimethylaminohydrolase 2. Circ Res. 2007. 101. 2-10.

18. Maas R. Pharmacotherapies and their influence on asymmetric dimethylargine (ADMA). Vasc Med. 2005.10. 49-57.

19. Kostourou V., Robinson S.P., Cartwright J.E., Whitley G.S. Dimethylarginine dimethylaminohydrolase I enhances tumor growth and angiogenesis. Br. J. Cancer. 2002. 87(6). 673-680.

20. Lee I.S., Nishikimi M., Inoue M., Muragaki Y., Ooshima A. Specific expression of alanineglyoxylate aminotransferase 2 in the epithelial cells of Henle's loop. Nephron. 1999. 83. 184-185.

21. Chen J.W., Hsu N.W., Wu T.C., Lin S.J., and Chang M. S. Long-term angiotensin-converting enzyme inhibition reduces plasma asymmetric

dimethylarginine and improves endothelial nitric oxide bioavailability and coronary microvascular function in patients with syndrome X. Am J Cardiol. 2002. 90. 974-982.

22. Zaripov, S. I., Umarova, Z. F., & Tursunova, L. D. (2022). The state of the quality of life of patients receiving program hemodialysis. Stein J.H., Patrick E., McBride P.E. Hyperhomocysteinemia and Atherosclerotic Vascular Disease Pathophysiology, Screening, and Treatment Arch Intern Med. 1998. 158 (12). 1301-1306. doi:10.1001/archinte.158.12.1301.

23. Manak N.A. Modern views on the prevention of coronary heart disease. Medical news. 2003. 5. 15-20.

24. Akhmedov, K. S., Rixsiyeva, L. M., Abdurahmanova, N. M., Botirbekov, A. N., Turaev, I. A., & Raximov, S. S. (2023). CHANGES IN C-TELOPEPTIDE COLLAGEN-II LEVEL IN PATIENTS WITH ANKYLOSING SPONDYLOARTHRITIS AFTER COVID-19. Journal of Modern Educational Achievements, 3(3), 78-87.

25. Zhloba A.A. The role of ADMA as an endogenous inhibitor of eNOS and one of the mediators of the development of vasomotor endothelial dysfunction. Regional circulation and microcirculation. 2007. 3. 4-14.

26. Abdurakhmanova N., Akhmedov K. AB0812 EFFECT OF PRO-INFLAMMATORY CYTOKINE-INTERLEUKIN 6 ON THE COURSE OF ANKYLOSING SPONDYLITIS IN PATIENTS AFTER COVID-19. – 2022.27. Kemeny-Beke A, Gesztelyi R, Bodnár N, Szántó S. Increased production of asymmetric dimethylarginine (ADMA) in ankylosing spondylitis: Association with other clinical and laboratory parameters. Joint, Bone, Spine. 2011. 78(2). 184-187. DOI:10.1016/j.jbspin.2010.05.009.

28. Erre G.L., Sanna P.S., Zinellu A., Ponchietti A., Fenu R., Sotgia S., Carru C., Ganau A., Passiu

29. Plasma asymmetric dimethylarginine (ADMA) levels and atherosclerotic disease in ankylosing spondylitis: a cross-sectional study. Clinical Rheumatology. 2011. 30 (1). 21-27. doi: 10.1007/s10067-010-1589-x.

30. Rakhimova M. et al. Endothelin-1biomarker Features In Patients With Ankylosing Spondylitis After COVID-19 //Journal of Positive School Psychology. – 2022. – C. 9369-9375.30. Poddubny D.A., Rebrov A.P. Hypertrophy and remodeling of the left ventricle in patients with ankylosing spondylitis: the role of endothelial dysfunction. Siberian Medical Journal. 2007. 7. 73-77.

РЕЗЮМЕ

СОВРЕМЕННЫЕ ПРЕДСТАВЛЕНИЯ ОБ ЭНДОТЕЛИАЛЬНОЙ ДИСФУНКЦИИ У БОЛЬНЫХ АНКИЛОЗИРУЮЩИМ СПОНДИЛОАРТРИТОМ

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В статье отражены современные представления об основных маркерах воспаления, вызывающих эндотелиальную дисфункцию, у больных анкилозирующим спондилоартритом. Особое внимание уделено роли асимметричного диметиларгинина в развитии сердечно-сосудистой патологии. Асимметричный диметиларгинин является структурным аналогом l-аргинина и ингибитором активности синтазы оксида азота. Оксид азота стимулирует дилатацию сосудов, снижает адгезию тромбоцитов, тем самым препятствуя развитию кардиоваскулярной патологии. В статье обобщены данные литературы о метаболизме диметиларгинина и его биологических эффектах на эндотелий. Приводятся сведения об увеличении уровней асимметричного диметиларгинина и гомоцистеина у больных анкилозирующим спондилитом и другими ревматическими заболеваниями. Считается, что повышенные плазменные концентрации данных соединений способствуют развитию дисфункции эндотелия и поддержанию системного воспаления. Однако до настоящего времени не установлено, является ли повышение уровня асимметричного диметиларгинина фактором, потенцирующим дисфункцию эндотелия, либо является одним из маркеров сердечно-сосудистой патологии. Проведенный ана- лиз литературы свидетельствует о необходимости дальнейших исследований в данной области.

Ключевые слова: анкилозирующий спондилоартрит, асимметричный диметиларгинин, гомоцистеин, дисфункция эндотелия, кардиоваскулярная патология.

SUMMARY

MODERN VIEW ON THE PROBLEM OF ENDOTHELIAL DYSFUNCTION IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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Summary. The article reflects modern concepts of the main inflammatory markers causing endothelial dysfunction in patients with ankylosing spondylitis. Particular attention is paid to the role of asymmetric dimethylarginine in the development of cardiovascular pathology. Asymmetric dimethylarginine is a structural analogue of l-arginine and an inhibitor of nitric oxide synthase activity. Nitric oxide stimulates the dilatation of blood vessels, reduces the adhesion of platelets, inhibiting the development of cardiovascular pathology. The article summarizes the literature data on the metabolism of dimethylarginine and its biological effects on the endothelium. The data about the increase of asymmetric dimethylarginine and homocysteine levels in patients with ankylosing spondylitis and other rheumatic diseases are presented. It is considered that the increased plasma concentrations of these compounds

contribute to the development of endothelial dysfunction and maintenance of systemic inflammation. Nowadays it has not been established yet whether the increase of asymmetric dimethylarginine level is a factor potentiating the endothelial dysfunction or only a marker of cardiovascular pathology. The literature analysis indicates the need for further research in this area.

Keywords: ankylosing spondylitis, asymmetric dimethylarginine, homocysteine, endothelial dysfunction, cardiovascular pathology.

УДК 544.72:547.96

ИЗУЧЕНИЕ МИКРОБИОЛОГИЧЕСКОЙ ЧИСТОТЫ СУБСТАНЦИИ С НАНОЧАСТИЦАМИ СЕРЕБРА

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Ключевые слова: Наночастицы серебра, экстракт, Scutellaria Iscandaria L., микробиологическая чистота, субстанция.

Актуальность. На сегодняшний день актуальной задачей в Республике Узбекистан является всестороннее развитие фармацевтической отрасли, направленное не только на улучшение качества промышленного производства готовых лекарственных форм, но и высокотехнологичное освоение производства современных субстанций на базе доступного местного сырья, разработка на их основе высокоэффективных конкурентноспособных на мировом рынке новых лекарственных средств.

При производстве субстанции и лекарственных субстанции и лекарственных средств необходимо изучить их микробиологической чистоты. Так, как безопасность лекарственного средства напрямую зависит от микробиологических показателей и с помощью этой методике можно оценивать и обеспечить их качества.

В статье представлены результаты изучения микробиологической чистоты субстанции «Сухой экстракт Травы Шлемник Искандарии с наночастицами серебра» в соответствии с Государственной Фармакопеей XI,вып.2, с.193 и Изменении №2 от 29.09.2005г. Категория №3.2.

Введение. В связи с интенсивными темпами развития наномедицины, появилась возможность использовать нанотехнологии в медицинской практике для модификации и разработки лекарственных средств, в том числе лекарственных субстанции на основе наночастиц открывающие большие перспективы для решения важнейших задач в области медицины и фармацевтики. В фармацевтической отрасли существует система обеспечения качества лекарственных средств и одним из наиболее важных параметров, характеризующих качество любой субстанций и лекарственных форм, является его микробиологическая чистота [1].