№78/2023

Znanstvena misel journal

The journal is registered and published in Slovenia.

ISSN 3124-1123

The frequency of publication – 12 times per year.

Journal is published in Slovenian, English, Polish, Russian, Ukrainian.

The format of the journal is A4, coated paper, matte laminated cover.

All articles are reviewed

Edition of journal does not carry responsibility for the materials published in a journal.

Sending the article to the editorial the author confirms it's uniqueness and takes full responsibility for possible consequences for breaking copyright laws

Free access to the electronic version of journal

Znanstvena misel journal

Slovenska cesta 8, 1000 Ljubljana, Slovenia

Email: info@znanstvena-journal.com

Website: www.znanstvena-journal.com

CONTENT

AGRICULTURAL SCIENCES

BIOLOGICAL SCIENCES

CHEMISTRY

ECONOMICS

MEDICAL SCIENCES

CORRELATION-REGRESSION ANALYSIS OF INDICATORS OF SYSTEMIC INFLAMMATION TAKING INTO ACCOUNT THE T-786C POLYMORPHISM OF THE ENOS GENE IN PATIENTS WITH RHEUMATOID ARTHRITIS WITH COMORBIDITY

Bukach O.,
assistant of the department of internal medicine
Tsola V.,
Pavliuk V.,
Plyska Y.
Bukovinian State Medical University

Abstract

Despite significant progress in establishing the causes, mechanisms of occurrence, approaches to diagnosis and treatment, rheumatoid arthritis (RA) remains one of the most widespread and prognostically unfavorable diseases. Early diagnosis of RA is difficult, since immunopathological changes with a subclinical course occur long before the appearance of clinical manifestations of the disease. Therefore, establishing a diagnosis in the first months of the disease is crucial for its further progression, prognosis and long-term consequences of RA. **Purpose:** to investigate the correlation-regression relationship of indicators of systemic inflammation, endothelial dysfunction, cytokine and lipid profiles of blood serum taking into account the *T-786C* polymorphism of the *eNOS* gene in patients with rheumatoid arthritis in combination with arterial hypertension (AH), abdominal obesity (AB) and type 2 diabetes (T2DM). **Materials and methods:** a laboratory and instrumental examination of 110 patients was carried out at the clinical base of the Department of Internal Medicine of the higher education institution of the Bukovyna State Medical University, Chernivtsi Regional Endocrinology Center, Chernivtsi Regional Clinical Hospital, and the State Institution "Reference Center for Molecular genetic research of the Ministry of Health of Ukraine". **Results:** In patients with RA with hypertension, AO, diabetes mellitus 2, a correlation was established between: the level of IL-10 and ACCP ($r=0.47$ $p<0.05$), IL-6 and ACCP ($r=0.60$ $p=0.006$), IL-18 and CRP ($r=-0.53$ $p<0.05$), total cholesterol and NO metabolites ($r=0.79$ $p<0.05$), HDL cholesterol and ET-1 ($r=-0.69$ $p<0.05$), HDL-C and CRP ($r=0.75$ $p<0.05$), HDL-C and ACCP ($r=0.50$ $p<0.05$), total cholesterol and ET- 1 ($r=0.56$ $p=0.058$). At the same time, in RA in the presence of *TC* genotype, a correlation was found between: CRP and HDL cholesterol ($r=0.56$ $p=0.005$), IL-12 and ET-1 ($r=0.53$ $p<0.05$), IL-10 and ACCP ($r=0.41$ $p=0.05$); in the presence of *TT* genotype - between total cholesterol and ACCP ($r=-0.37$ $p=0.05$); in the presence of *CC* genotype - between total cholesterol and ET-1 ($r=0.92$ $p<0.05$), HDL cholesterol and ET-1 ($r=0.86$ $p<0.05$), IL-18 and CRP ($r=-0.72$; $p<0.05$), IL-10 and ET-1 ($r=0.86$ $p<0.05$). **Conclusions.** The obtained results indicate the presence of correlations between indicators of systemic inflammation, endothelial function and dyslipidemia in RA patients with comorbid pathology, taking into account genetic predictors.

Keywords: rheumatoid arthritis, lipid metabolism, cytokine profile, inflammatory markers, *T-786C eNOS* gene polymorphism, comorbid pathology.

Introduction. It should be noted that the most common cause of death in economically developed countries are cardiovascular diseases (ischemic heart disease (CHD), myocardial infarction (MI), atherosclerosis, strokes). And if MI is a frequent cause of premature death among people under the age of 55 [1, 2, 3], then a high level of cardiovascular comorbidity, especially coronary heart disease, is the most significant predictor of premature death in patients with rheumatoid arthritis (RA) [4, 5]. Separate studies have established a connection between RA and CHD through a systemic inflammatory response [6], and it has also been suggested that CHD is a manifestation of extra-articular RA, provoked by an active inflammatory process, drug exposure, or other secondary factors [7]. However, it could be CHD and RA separately, which had common clinical symptoms and pathogenetic background, the most prominent of which was the chronic inflammatory process and endothelial dysfunction (ED), regardless of its localization.

In recent years, scientists have discovered dozens of new areas in the human genome associated with rheumatoid arthritis and found out that certain candidate genes play an important role in the development and progression of RA [8, 9], which requires the search for new approaches to prevention and treatment of this disease [10, 11].

According to the research of A. Yarwood et al. [12], a close relationship was established between the development of RA and antigens of the histocompatibility system HLA DR1 DR4 DRW4, DW4, DW14.

However, other genetic associations that affect the severity of RA are known, namely the gene encoding TNF-a, specific genes for immunoglobulins, IL-1, IL-3, IL-4, and IL-10 [13]. Some scientists believe that the *T786C eNOS* gene promoter polymorphism affects the course of reparative osteogenesis [14], however, this polymorphism was studied most often as a risk factor for cardiovascular diseases, namely the occurrence of CHD [15, 16, 17, 18].

On the other hand, the study of the role of the *T-786C* polymorphism of the *eNOS* gene promoter in the formation of RA in the Ukrainian population was not previously conducted, and the data available abroad are contradictory [19]. Therefore, the study of molecular genetic predictors in the development of RA associated with arterial hypertension (AH), abdominal obesity

(AB) and type 2 diabetes mellitus (T2DM) is a very relevant issue today, which will create prerequisites for the development of primary and secondary prevention and individualized complex treatment.

Material and methods. All patients underwent a complex of examinations: general clinical, anthropometric, spectrophotometric (lipid spectrum of blood (total cholesterol (TH), triacylglycerol (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C)), colorimetric (total stable metabolites of NO), immunoenzymatic (content of endothelin-1 (ET-1), C-reactive protein (CRP), rheumatoid factor (RF), antibodies to cyclic citrulline peptide (ACCP), IL-6, IL-12, IL -18, IL-10), molecular genetic (polymorphism *T-786C* of the *eNOS* gene promoter).

Statistical processing was carried out using Microsoft Office Excel® 2007™, IBM SPSS Statistics® 23.0 applications. In the statistical analysis of the quantitative results of the study, arithmetic mean values (M) and standard error (m) were calculated. Data are given as M±m. Correlation was calculated using Pearson's linear parametric correlation coefficient and Spearman's nonparametric rank correlation coefficient.

Research results and discussion.

The analysis of correlations (r) of the blood lipid spectrum with indicators of inflammation and endothelial dysfunction in patients with RA in combination with hypertension, AO and diabetes 2, depending on the *T-786C* polymorphism of the *eNOS* gene is shown in table 1.

Correlation analysis proved a direct, medium-strength relationship between the level of CRP and HDL cholesterol in *TC*-genotype carriers (r=0.56 p=0.005), while in *TT*-genotype carriers, an inverse correlation between CRP and HDL cholesterol was established (r=-0.37 p=0.05). In carriers of the *CC* genotype, the level of cholesterol and HDL cholesterol directly depended on the content of ET-1 (r=0.92 p<0.05) and HDL cholesterol (r=0.86 p<0.05), respectively.

Table 1

Relationships (r) of the blood lipid spectrum with indicators of inflammation and endothelial dysfunction in patients with RA depending on the *T-786C* polymorphism of the *eNOS* gene

Genotypes of the eNOS gene in patients	Indexes	CRP	ACCP	ET-1	The total level of stable NO metabolites
TT	TH	r=-0,22 p>0,05	r=-0,37 p=0,05	r=0,04 p>0,05	r=0,02 p>0,05
	TG	r=-0,06 p>0,05	r=-0,19 p>0,05	r=0,04 p>0,05	r=-0,16 p>0,05
	HDL-C	r=-0,10 p>0,05	r=0,16 p>0,05	r=0,04 p>0,05	r=-0,28 p>0,05
	LDL-C	r=-0,10 p>0,05	r=-0,10 p>0,05	r=-0,09 p>0,05	r=-0,09 p>0,05
TC	TH	r=0,16 p>0,05	r=0,07 p>0,05	r=-0,003 p>0,05	r=0,40 p>0,05
	TG	r=-0,38 p>0,05	r=-0,14 p>0,05	r=-0,12 p>0,05	r=-0,24 p>0,05
	HDL-C	r=0,56 p=0,005	r=0,38 p>0,05	r=0,48 p>0,05	r=-0,08 p>0,05
	LDL-C	r=-0,17 p>0,05	r=0,09 p>0,05	r=0,08 p>0,05	r=-0,08 p>0,05
CC	TH	r=-0,29 p>0,05	r=0,22 p>0,05	r=0,92 p<0,05	r=0,51 p>0,05
	TG	r=0,58 p>0,05	r=0,43 p>0,05	r=0,32 p>0,05	r=0,60 p>0,05
	HDL-C	r=-0,25 p>0,05	r=0,30 p>0,05	r=0,86 p<0,05	r=0,73 p>0,05
	LDL-C	r=-0,36 p>0,05	r=0,07 p>0,05	r=0,65 p>0,05	r=0,02 p>0,05

Note. TH - total cholesterol; TG – triacylglycerol; HDL/LDL cholesterol – cholesterol of high/low density lipoproteins; CRP - C-reactive protein; ACCP – antibodies to cyclic citrulline peptide; ET-1 - endothelin-1.

Relationships (r) of the cytokine profile with indicators of inflammation and endothelial dysfunction in patients with RA depending on the *T-786C* polymorphism of the *eNOS* gene are shown in table. 2. In carriers of the *TC* genotype, a close relationship between the level of IL-12 and the level of ET-1 (r=0.53 p<0.05), as well as between IL-10 and ACCP (r=0.41 p =0.05). When assessing the correlation, the level of IL-18 was inversely correlated with CRP (r=-0.72; p<0.05), and the level of IL-10 directly depended on the content of ET-1 (r=0.86 p<0.05) in carriers of the *CC* genotype.

Table 2

Relationships of the cytokine profile with indicators of inflammation and endothelial dysfunction in patients with RA depending on the *T-786C* polymorphism of the *eNOS* gene

Genotypes of the *eNOS* gene in patients	In-dexes	CRP	ACCP	ET-1	The total level of stable NO metabolites
TT	IL-12	r=0,02 p>0,05	r=0,07 p>0,05	r=-0,07 p>0,05	r=0,07 p>0,05
	IL-18	r=-0,23 p>0,05	r=-0,004 p>0,05	r=-0,28 p>0,05	r=0,12 p>0,05
	IL-10	r=-0,34 p>0,05	r=0,13 p>0,05	r=0,13 p>0,05	r=0,03 p>0,05
	IL-6	r=-0,17 p>0,05	r=0,21 p>0,05	r=-0,18 p>0,05	r=-0,13 p>0,05
TC	IL-12	r=0,26 p>0,05	r=-0,08 p>0,05	r=0,53 p<0,05	r=0,21 p>0,05
	IL-18	r=-0,19 p>0,05	r=-0,19 p>0,05	r=-0,12 p>0,05	r=0,14 p>0,05
	IL-10	r=0,02 p>0,05	r=0,41 p=0,05	r=-0,18 p>0,05	r=0,36 p>0,05
	IL-6	r=0,26 p>0,05	r=0,16 p>0,05	r=-0,03 p>0,05	r=0,11 p>0,05
CC	IL-12	r=0,49 p>0,05	r=-0,38 p>0,05	r=-0,44 p>0,05	r=-0,25 p>0,05
	IL-18	r=-0,72 p<0,05	r=-0,06 p>0,05	r=-0,12 p>0,05	r=-0,54 p>0,05
	IL-10	r=-0,22 p>0,05	r=0,35 p>0,05	r=0,86 p<0,05	r=0,42 p>0,05
	IL-6	r=0,06 p>0,05	r=-0,02 p>0,05	r=-0,63 p>0,05	r=-0,19 p>0,05

Note. IL-interleukin; CRP–C-reactive protein; ACCP–antibodies to cyclic citrulline peptide; ET-1 - endothelin-1.

In patients with RA with comorbid pathology, a close relationship with the level of TH and HDL-C was observed (Table 3). Analyzing the obtained data, in patients with RA in combination with hypertension, AO and diabetes mellitus 2, a close relationship between TH and NO metabolites was revealed (r=0.79 p<0.05), the level of HDL-C was inversely correlated with the content of ET-1 (r=-0.69 p<0.05) and directly depended on the level of CRP (r=0.75 p<0.05). The presence of a direct correlation between HDL-C and the level of ET-1 and ACCP (r=0.52 p<0.05) and (r=0.50 p<0.05), respectively, was also revealed. It should be noted that there is a direct relationship between TH and ET-1 (r=0.56, p=0.058) in patients with RA in combination with AO, hypertension, and type 2 diabetes.

Table 3

Correlations of lipid metabolism with indicators of inflammation and endothelial dysfunction in patients with RA depending on comorbid pathology

Pathology	In-dexes	CRP	ACCP	ET-1	The total level of stable NO metabolites
RA	CHL	r=0,04 p>0,05	r=-0,27 p>0,05	r=-0,004 p>0,05	r=-0,44 p>0,05
	TG	r=-0,31 p>0,05	r=0,18 p>0,05	r=-0,25 p>0,05	r=0,12 p>0,05
	HDL-C	r=0,18 p>0,05	r=0,22 p>0,05	r=-0,15 p>0,05	r=-0,11 p>0,05
	LDL-C	r=0,06 p>0,05	r=0,08 p>0,05	r=-0,05 p>0,05	r=-0,23 p>0,05
RA with AH	CHL	r=-0,61 p>0,05	r=0,14 p>0,05	r=-0,18 p>0,05	r=-0,05 p>0,05
	TG	r=-0,59 p>0,05	r=-0,50 p>0,05	r=0,05 p>0,05	r=0,23 p>0,05
	HDL-C	r=-0,17 p>0,05	r=0,53 p>0,05	r=0,52 p<0,05	r=-0,26 p>0,05
	LDL-C	r=-0,09 p>0,05	r=0,47 p>0,05	r=0,003 p>0,05	r=-0,46 p>0,05
RA with AH and AO	CHL	r=-0,17 p>0,05	r=-0,16 p>0,05	r=0,09 p>0,05	r=-0,06 p>0,05
	TG	r=-0,46 p>0,05	r=-0,07 p>0,05	r=0,17 p>0,05	r=-0,42 p>0,05
	HDL-C	r=0,11 p>0,05	r=-0,09 p>0,05	r=0,23 p<0,05	r=-0,33 p>0,05
	LDL-C	r=-0,36 p>0,05	r=0,04 p>0,05	r=0,34 p>0,05	r=-0,33 p>0,05
RA with AH, AO and DM 2	CHL	r=-0,09 p>0,05	r=-0,04 p>0,05	r=0,56 p=0,058	r=0,79 p<0,05
	TG	r=0,10 p>0,05	r=-0,42 p>0,05	r=-0,05 p>0,05	r=0,02 p>0,05
	HDL-C	r=0,75 p<0,05	r=0,50 p<0,05	r=-0,69 p<0,05	r=0,40 p>0,05
	LDL-C	r=-0,11 p>0,05	r=-0,25 p>0,05	r=0,11 p>0,05	r=-0,17 p>0,05

Note. TH - total cholesterol; TG – triacylglycerol; HDL/LDL cholesterol – cholesterol of high/low density lipoproteins; CRP - C-reactive protein; ACCP – antibodies to cyclic citrulline peptide; ET-1 - endothelin-1.

According to the correlation-regression analysis, we established a close relationship between the cytokine profile and the level of acute phase indicators in RA patients with comorbid pathology (Table 4). In patients with RA, a close relationship of medium strength was found between the level of IL-10 and ACCP (r=0.47 p<0.05), and in patients with RA in combination with hypertension, AO, and diabetes 2, a direct relationship between IL- 6 and ACCP (r=0.60 p=0.006). An inverse correlation was established between IL-18 and CRP in RA patients in combination with hypertension, AO and diabetes 2 (r=-0.53 p<0.05) (Table 4).

Table 4

Correlations of the cytokine profile with indicators of inflammation and endothelial dysfunction in patients with RA depending on comorbid pathology

Pathology	In-dexes	CRP	ACCP	ET-1	The total level of stable NO metabolites
RA	ІЛ-12	r=0,24 p>0,05	r=-0,18 p>0,05	r=-0,12 p>0,05	r=0,004 p>0,05
	ІЛ-18	r=-0,25 p>0,05	r=-0,02 p>0,05	r=-0,08 p>0,05	r=0,41 p>0,05
	ІЛ-10	r=-0,23 p>0,05	r=0,47 p<0,05	r=-0,23 p>0,05	r=0,10 p>0,05
	ІЛ-6	r=0,21 p>0,05	r=0,25 p>0,05	r=0,32 p>0,05	r=0,09 p>0,05
RA with AH	ІЛ-12	r=0,38 p>0,05	r=-0,02 p>0,05	r=-0,03 p>0,05	r=-0,13 p>0,05
	ІЛ-18	r=-0,49 p>0,05	r=-0,16 p>0,05	r=-0,33 p>0,05	r=0,71 p>0,05
	ІЛ-10	r=-0,24 p>0,05	r=0,61 p>0,05	r=-0,35 p>0,05	r=0,57 p>0,05
	ІЛ-6	r=0,04 p>0,05	r=-0,20 p>0,05	r=0,46 p>0,05	r=-0,46 p>0,05
RA with AH and AO	ІЛ-12	r=-0,02 p>0,05	r=0,04 p>0,05	r=0,25 p>0,05	r=0,11 p>0,05
	ІЛ-18	r=-0,07 p>0,05	r=-0,36 p>0,05	r=-0,13 p>0,05	r=0,04 p>0,05
	ІЛ-10	r=-0,21 p>0,05	r=-0,04 p>0,05	r=0,21 p<0,05	r=0,06 p>0,05
	ІЛ-6	r=0,05 p>0,05	r=-0,46 p>0,05	r=-0,13 p>0,05	r=0,07 p>0,05
RA with AH, AO and DM 2	ІЛ-12	r=0,30 p>0,05	r=0,05 p>0,05	r=-0,13 p>0,05	r=-0,07 p>0,05
	ІЛ-18	r=-0,53 p<0,05	r=0,13 p>0,05	r=-0,02 p>0,05	r=-0,01 p>0,05
	ІЛ-10	r=-0,18 p>0,05	r=0,47 p<0,05	r=-0,19 p>0,05	r=0,14 p>0,05
	ІЛ-6	r=0,06 p>0,05	r=0,60 p=0,01	r=-0,02 p>0,05	r=-0,03 p>0,05

Note. IL-interleukin; CRP–C-reactive protein; ACCP – antibodies to cyclic citrulline peptide; ET-1-endothelin-1.

Through correlation analysis, in patients with RA with comorbid pathology, a close direct and inverse relationship was established between: the level of IL-10 and ACCP (r=0.47 p<0.05), IL-6 and ACCP (r=0.60 p=0.006), IL-18 and CRP (r=-0.53 p<0.05), TH and stable NO metabolites (r=0.79 p<0.05), HDL cholesterol and ET-1 (r =-0.69 p<0.05), HDL-C and CRP (r=0.75 p<0.05), HDL-C and ACCP (r=0.50 p<0.05), TH and ET- 1 (r=0.56 p=0.058). Taking into account the polymorphic variants of the *T-786C eNOS* gene, a positive and negative correlation was found between: CRP and HDL cholesterol (r=0.56 p=0.005), IL-12 and ET-1 (r=0.53 p<0, 05), IL-10 and ACCP (r=0.41 p=0.05) in *TC*-genotype carriers; TH and ACCP (r=-0.37 p=0.05) in carriers of the *TT* genotype, TH and ET-1 (r=0.92 p<0.05), HDL C and ET-1 (r=0 .86 p<0.05), IL-18 and CRP (r=-0.72; p<0.05), IL-10 and ET-1 (r=0.86 p<0.05) in carriers mutant *CC* genotype, which can be explained by the strengthening of the systemic inflammatory response to "damage" and the mutually aggravating effect of comorbid pathology on the course of RA.

Conclusion. The obtained results indicate the presence of correlations between indicators of systemic inflammation, endothelial function and dyslipidemia in RA patients with comorbid pathology, taking into account genetic predictors.

References

1. Федчишин НЄ. Хвороби системи кровообігу: динаміка поширеності в Україні та Тернопільській області. Вісник соціальної гігієни та організації охорони здоров'я України. 2013;1:53-5.

2. Choi BJ, Prasad A, Gulati R, Best PJ, Lennon RJ, Barsness GW, et al. Coronary endothelial dysfunction in patients with early coronary artery disease is associated with the increase in intravascular lipid core plaque. Eur Heart J. 2013 Jul;34(27):2047-54. doi: 10.1093/eurheartj/eht132.

3. Huffman MD, Lloyd-Jones DM, Ning H, Labarthe DR, Ford ES, Capewell S. Quantifying Options for Reducing Coronary Heart Disease Mortality By 2020. Circulation. 2013 Jun 25;127(25):2477-84. doi: 10.1161/CIRCULATIONAHA.112.000769.

4. Dadoun S, Zeboulon-Ktorza N, Combescure C, Elhai M, Rozenberg S, Gossec L *et al*. Mortality in rheumatoid arthritis over the last fifty years: systematic

review and meta-analysis. Joint Bone Spine. 2013;80:29–33. doi:10.1016/j.jbspin.2012.02.005.

5. Lezcano-Valverde JM. Salazar F, León L, Toledano E, Jover JA., Fernandez-Gutierrez B et al. Development and validation of a multivariate predictive model for rheumatoid arthritis mortality using a machine learning approach. Scientific Reports/ 2017 Dec;7(1):1-10. doi 10.1038/s41598-017-10558-w.

6. Snow MH, Mikuls TR. Rheumatoid arthritis and cardiovascular disease: the role of systemic inflammation and evolving strategies of prevention. Curr Opin Rheumatol. 2005 May;17(3):234-41.

7. Wolfe F, Freundlich B, Straus WL. Increase in cardiovascular and cerebrovascular disease prevalence in rheumatoid arthritis. J Rheumatol. 2003 Jan;30(1):36-40.

8. Savchenko OV. BCL1 polymorphism of glucocorticoids receptor gene in patients with rheumatoid arthritis. J Clin Exp Med Res. 2015;3(2):271-6.

9. Almutairi KB, Nossent JC, Preen DB, Keen HI, Inderjeeth CA. The prevalence of Rheumatoid Arthritis: A systematic review of population-based studies. The Journal of rheumatology. 2021;48(5): 669–676. doi: 10.3899/jrheum.200367.

10. Процюк ЛО. Поліморфізм гена серотонінових рецепторів (5-HTR2A) і його зв'язок з ефективністю лікування хворих на ревматоїдний артрит. Одеський медичний журнал. 2016;4(156):29-36.

11. Janke K, Biester K, Krause D, Richter B, Schürmann C, Hirsch K. et al. Comparative effectiveness of biological medicines in rheumatoid arthritis: systematic review and network meta-analysis including aggregate results from reanalysed individual patient data. BMJ. 2020;370:m2288. Jul. 7. doi: 10.1136/bmj.m2288 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7338922.

12. Yarwood A, Huizinga TWJ, Worthington J. The genetics of rheumatoid arthritis: risk and protection in different stages of the evolution of RA. Rheumatology, Volume 55, Issue 2, 1 February 2016, Pages 199–209,https://doi.org/10.1093/rheumatology/keu323.

13. Dessie G, Tadesse Y, Demelash B, Genet S. Assessment of Serum Lipid Profiles and High-sensitivity C-reactive Protein Among Patients Suffering from Rheumatoid Arthritis at Tikur Anbessa. Specialized Hospital, Addis Ababa, Ethiopia: A Cross-Sectional Study. Open Access Rheumatol. 2020; 12:223–232. PMID: 33061690. PMCID: PMC7520147. doi: 10.2147/OARRR.S264466.

14. Безсмертний ЮО. Поширеність мутації промотора гена eNOS T786C у хворих із хибними суглобами довгих кісток: зв’язок із рівнем гомоцистеїну та медіаторами запалення. Травма. 2013;14(2):85-9.

15. Воронков ЛГ, Горовенко НГ, Мазур ІД, Шкурат АІ, Мхітарян ЛС, Орлова НМ. Поліморфні варіанти Т (–786) С і G894T гена ендотеліальної NO-синтази та стан вазодилатаційної функції ендотелію у хворих із хронічною серцевою недостатністю. Серце і судини. 2012;4:43-51.

16. Приступа ЛН, Погорєлова ОС. Асоціація алельних поліморфізмів гену ендотеліальної NO-синтази з розвитком ішемічної хвороби серця. Журнал клінічних та експерементальних медичних досліджень. 2015;3(3):375-86.

17. Rai H, Parveen F, Kumar S, Kapoor A, Sinha N. Association of endothelial nitric oxide synthase gene polymorphisms with coronary artery disease: An Updated Meta-Analysis and Systematic Review. Plos One. 2014 Nov 19;9(11):e113363. doi: 10.1371/journal.pone.0113363.

18. Хіміон ЛВ, Кузик ІО. Nt-proBNP у хворих на ревматоїдний артрит молодого віку: взаємозв’язок із клініко-лабораторними характеристиками артриту та атеросклеротичним процесом. Український ревматологічний журнал. 2021; 83(1): 19–26.

19. Kong, X.Z., Zhang, Z.Y., Wei, L.H., Li, R., Yu, J. The endothelial nitric oxide synthase gene T-786C polymorphism increases myocardial infarction risk: A meta-analysis, Med SciMonit, 2017, vol. 23, pp. 759–766. doi: 10.12659/MSM.899905.