ORIGINAL ARTICLE

CONTENTS

Effect of deficiency of natural anticoagulants on clinical heterogeneity of rheumatoid arthritis

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ABSTRACT

Aim: To investigate the concentration of natural anticoagulants protein C (PC) and tissue plasminogen activator (t-PA) in patients with rheumatoid arthritis (RA) and to evaluate the effect of their concentration on the course of the disease.

Materials and Methods: We examined 74 patients with RA. There were 15 men and 59 women and control group consisted of 27 subjects. The average age of the patients was 47.3±1.12 years. Laboratory (PC, t-PA, C-reactive protein, TNF-alpha, von Willebrand factor, and lipid profile) and instrumental (ultrasonography and Doppler) examinations were performed.

Results: PC deficiency was significantly more common among men with RA (26.6%), but did not depend on the age and the duration of the disease ($p<0.05$). PC deficiency correlates with the degree of activity of the inflammatory process ($r = -0.27$) and TNF-alpha ($r = -0.37$). The levels of PC and t-PA were associated with the level of cholesterol ($r = -0.25$), LDL-C ($r = -0.31$), and HDL-C ($r = 0.31$). In patients with PC and t-PA deficiency, significantly higher (by 19% and 12%, respectively) serum levels of Von Willebrand factor were recorded than in patients with normal levels ($p<0.05$).

Conclusions: The study of PC and t-PA revealed a deficiency of important natural anticoagulants, that helps us to expand the understanding of the mutually aggravating effect of the deficiency of these compounds and changes in known biologically active substances on the course of RA, and to supplement the pathogenetic picture of RA with certain links.

KEY WORDS: rheumatoid arthritis, protein C, tissue plasminogen activator

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INTRODUCTION

Difficulties in the timely diagnosis of rheumatoid arthritis (RA), which is considered one of the models of chronic inflammatory diseases, are not always due to the pathognomonic symptoms of the initial period of the disease, which may remain unnoticed by specialists for some time [1]. In the context of understanding the clinical heterogeneity of the disease, the search for new links in the pathogenesis of both RA and its systemic manifestations continues. Studies of immunologic disorders in RA open up significant prospects for improving the methods of diagnosis and treatment of various clinical variants of this disease.

In particular, the mechanisms of hyperproduction of interleukin-2, interferon γ, interleukin-17; imbalance between proinflammatory (tumor necrosis factor alpha (TNF-alpha), interleukin-1β, interleukin-6 (IL-6), interleukin-8, etc.) and anti-inflammatory cytokines (interleukin-4, interleukin-10, soluble interleukin-1β antagonist, etc.) with the production of the former over the latter are understood. It has been established that the synthesis of TNF-alpha predominates in the onset of the disease, and its uncontrolled synthesis underlies the chronicization of the pathological process and progressive bone destructive changes. TNF-alpha is involved in the development of clinical signs of inflammation, induces the expression of adhesion molecules, stimulates neoangiogenesis, fibroblast proliferation, which play a key role in the formation of the rheumatoid pannus [2].

However, the increase in the number of vascular systemic manifestations in the population of patients with RA, especially among male patients, indicates the need to identify the nature of changes in both

the vascular wall and the hemostatic system and to determine the role of these changes in the multidirectional pathways of RA progression. One of the important components of systemic hemostasis, which is also involved in the regulation of the human immune system in response to vascular or inflammatory damage, is the protein C (PC) system. Its activated form has strong anticoagulant activity. Also, activated PC has cytoprotective and anti-inflammatory effects on vascular endothelial cells, neuronal cells, and various cells of the human immune system [3, 4].

Since 1960, when PC was discovered by Professor Seegers, scientists have described numerous properties of this substance. There are about 20 genes known to be upregulated by activated PC and 20 genes known to be downregulated by activated PC. The former include genes with anti-inflammatory and anti-apoptotic activity, and the latter - with pro-inflammatory and pro-apoptotic activity. Another important function of activated PC is the ability to accelerate plasminogen-dependent thrombus lysis, which is a direct manifestation of its angioprotective properties [3, 5].

AIM

The aim of our study was to investigate the concentration of natural anticoagulants PC and tissue plasminogen activator (t-PA) in patients with RA and to evaluate the effect of their concentration on the course of the disease.

MATERIALS AND METHODS

We observed 74 patients with RA. There were 15 men (20.3%) and 59 women (79.7%). The control group consisted of 27 people of comparable age and gender. The average age of patients was 47.3±1.12 years.

RA was diagnosed based according to the American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) 2010 criteria [6].

Exclusion criteria: Pregnancy, patients with liver disease, vitamin K deficiency, metastatic tumors, ICE syndrome, fresh thrombosis, severe bacterial infection at a young age, nephrotic syndrome, homocysteinuria, patients treated with warfarin and other indirect anticoagulants, prolonged antibiotic therapy with insufficient food intake, oral contraceptives.

The content of C-reactive protein (CRP), TNF-alpha and Von Willebrand factor (VWF) in the blood was determined by enzyme-linked immunosorbent assay using standard kits from «Diagnostic Automation Inc.», USA, "Calbiotech", Germany and "Shield diagnostics", England.

The activity of PC was determined using a PC activator derived from the venom of the common scabies (Agkistrodon halys) using the chromogenic substrate S236 [7, 8]. The potential of the fibrinolytic system was assessed by the activity of t-PA [9].

Serum levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were measured according to standard methods. The value of low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula: LDL-C=TC-HDL-C-0.45*TG.

To study endothelial function, high-resolution echolocation and Doppler ultrasonography of the brachial artery were used as described by Celermajer D. et al. (1992). The thickness of the intima-media complex (IMC) was determined by scanning the common carotid artery (CCA) in B-mode echolocation at a distance of 2 cm from the bifurcation in the diastolic phase at maximum magnification. The degree of atherosclerotic vascular lesions and the presence of atherosclerotic plaques were assessed by Wendelhag I. et al. (1993) [10].

Data analysis was performed in SPSS Statistics v.23. Summary statistics of mean, standard deviation and percentiles were used for quantitative measurements. The association between measures was assessed using the correlation test and t-test. The probability value was estimated at 0.05 confidence level (P=0.05).

RESULTS

A comparative analysis of the frequency of certain disorders in the hemostatic system in patients with RA and practically healthy subjects revealed some differences (Table 1). In particular, the average level of the natural anticoagulant PS in patients with RA was 10.6% lower compared with controls, and the proportion of patients with PS deficiency was 2.5 times higher, respectively. Analysis of the state of the fibrinolytic system in patients with RA revealed a significant suppression of its activity, which was manifested by a decrease in the content of t-PA. In particular, the average level of t-PA in patients with RA was 17.4% lower than in the control group, and the proportion of people with its deficiency was 36%, while in the control group it was only 11.1%. No gender differences were found in the frequency of disorders and mean values of t-PA levels, while men were significantly more likely to have a PC deficiency compared with women.

A comparative analysis of the studied hemostatic parameters in patients with RA depending on age

Table 1. Ranking of PC and t-PA levels in patients with RA and control group, their relationship with gender, age, disease duration and BMI

		PC		t-PA	
		Abs. value, (M±m)	**PC deficiency ≤70 %**	**Abs. value, (M±m)**	**t-PA deficiency ≤ 1,7 IU/ml**
1	Control group, n=27	94,6±1,39	2 (7,4%)	2,02±0,03	3 (11,1%)
2	Patients with RA, n=74	85,53±1,47$^{\beta}$	14 (18,9%)$^{\beta}$	1,72±0,05$^{\beta}$	27 (36%)$^{\beta}$
	Including				
3	Women with RA, n=59	85,52±1,63	10 (16,9%)	1,69±0,06	21 (35,6%)
4	Men with RA, n=15	84,53±3,51	4 (26,6%)*	1,85±0,10	6 (40%)
	Connection with the age of patients with RA				
5	≤ 35 years, n=6	90,17±5,54	1 (16,6%)	1,86±0,19	2 (33,3%)
6	36-50 years, n=31	87,59±2,35	5 (16,2%)	1,77±0,08	9 (29,0%)
7	> 50 years, n=37	84,76±1,93	8 (21,6%)	1,66±0,08	16 (43,2%)
	Dependence on the duration of the disease				
8	< 5 years, n=25	87,80±2,57	5 (20,0%)	1,66±0,08	6 (24,0%)
9	5-10 years, n=15	85,73±3,43	4 (26,6%)	1,88±0,10	7 (46,6%)
10	>10 years, n=34	83,76±2,12	5 (14,7%)	1,66±0,07	14 (41,2%)
	Connection with BMI of patients with RA				
11	BMI<30, n=55	86,04±1,72	9 (16,4%)	1,76±0,06	18 (30,9%)
12	BMI>30, n=19	84,05±1,47	5 (26,3%)§	1,60±0,06	9 (52,6%)§

Note: p<0.05, * - significant difference in women with RA, § - in patients with RA with BMI <30, β - compared to the control group.

Table 2. Ranking of PC and t-PA levels in patients with RA depending on the indicators of lipid metabolism

	Lipid levels	**PC**		**t-PA**	
		(M±m)	**r**	**(M±m)**	**r**
TC, mmol/l	Optimal, n=23	90,04±2,36	-0,27$^{\pi}$	1,85±0,09	-0,25$^{\pi}$
	Extremely elevated, n=28	86,93±2,44		1,74±0,09	
	High, n=23	79,30±2,44*§		1,57±1,10*	
HDL-C, mmol/l	Normal, n=19	87,68±2,50	0,19	1,85±0,08	0,31$^{\pi}$
	Subnormal, n=11	89,36±3,51		1,96±0,11	
	Low, n=44	83,64±2,06		1,60±0,07$^{\#\alpha}$	
LDL-C, mmol/l	Normal, n=33	87,55±2,04	-0,26$^{\pi}$	1,78±0,07	-0,31$^{\pi}$
	Extremely elevated, n=12	92,17±3,61		1,84±0,16	
	High, n=29	80,48±2,28$^{¥£}$		1,60±0,09	
TG, mmol/l	Normal, n=15	89,33±3,11	-0,21	1,84±1,11	-0,24
	Extremely elevated, n=31	84,94±1,14		1,73±0,08	
	High, n=37	84,65±2,18		1,68±0,08	

Note: p<0.05, * - significant difference compared to the group "optimal TC level"; § - to the group "extremely elevated TC level"; # - to the group "normal HDL-C level"; α - to the group "subnormal HDL-C level"; ¥ - to the group "normal LDL-C level"; £ - to the group "extremely elevated LDL-C level"; π - significant values of the correlation coefficient.

revealed that PC and t-PA deficiency is inherent in all age categories. Disorders in the hemostatic system in patients with RA also had no relationship with the duration of the disease, as indicated by the almost equal proportion of patients with PC and t-PA deficiency among patients with a disease duration of up to 5 years and more than 10 years. At the same time, PC and t-PA levels were associated with body mass index (BMI). In particular, in the group of patients with a BMI > 30, the proportion of patients with PC and t-PA deficiency was 1.6 and 1.7 times higher, respectively, than in patients with a BMI < 30.

The analysis showed that the levels of PC and t-PA were associated with the lipid spectrum of serum in patients

Table 3. Serum levels of PS and t-PA in patients with RA depending on inflammatory process activity

			PC		t-PA	
			(M±m)	r	(M±m)	r
1	CRP, mg/l	≤ 25 percentile, n=20	88,30±2,51	-0,34#	1,92±0,07	-0,32#
		>25≤75 percentile, n=30	88,03±2,29		1,73±0,09	
		>75 percentile, n=24	80,08±2,60*§		1,54±0,10*	
2	TNF-alpha, pg/ml	≤ 25 percentile, n=16	89,88±2,62	-0,37#	2,22±0,07	-0,40#
		>25≤75 percentile, n=33	85,67±2,24		1,68±0,08*	
		>75 percentile, n=22	80,77±2,83*		1,54±0,11*	
3	ESR, mm/h	≤ 25 percentile, n=18	88,56±2,50	-0,27#	1,91±0,06	-0,30#
		>25≤75 percentile, n=30	88,90±2,29		1,80±0,08	
		>75 percentile, n=26	79,54±2,42*§		1,50±0,10*§	
4	DAS_{28}, points	≤ 25 percentile, n=20	87,55±2,38	-0,14	1,88±0,06	-0,28#
		>25≤75 percentile, n=25	84,08±2,85		1,68±0,10	
		>75 percentile, n=29	84,62±0,72		1,64±0,09*	

Note: p<0.05, * - significant difference compared to the group "<25 percentile"; § - to the group ">25≤75 percentile"; #- significant values of the correlation coefficient.

Table 4. Levels of PC and t-PA depending on subclinical manifestations of atherosclerotic vascular lesions and serum levels of VWF in patients with RA (M±m)

		PC		t-PA	
		Normal level, n=60	Low level, ≤70 %, n=14	Normal level, n=47	Lower than 1,7 IU/ml, n=27
IMC CCA (mm)		0,81±0,03	0,95±0,08	0,76±0,03	0,98±0,05*
Number of subjects with IMC CCA>0,90 mm, n (%)		31 (51,7%)	8 (57,1%)*	14 (29,8%)	17 (62,9%)*
EDVBA, %		5,31±0,67*	2,47±1,46*	6,05±0,81	2,53±0,80*
Число осіб з EDVBA ≤8,0%, n (%)		40 (66,6%)	11 (78,6%)	27 (57,4%)	24 (88,8%)*
Presence of atherosclerotic plaques		18 (30%)	8 (57,1%)*	12 (25,5%)	14 (51,9%)*
Lesions of CCA by Wendelhag scale, n (%)	0	42 (70%)	6 (42,8%)*	35 (74,5%)	13 (48,1%)*
	1	15 (25%)	6 (42,8%)*	9 (19,2%)	12 (44,4%)
	2	3 (5%)	1 (7,2%)*	3 (6,3%)	1 (3,7%)
	3	0 (0%)	1 (7,2%)	0 (0%)	1 (3,7%)
VWF		150,4±6,83	178,6±6,68*	157,6±5,91	175,9±9,58*

Note: p<0,05, *- significant difference compared to subjects with normal level of PC and t-PA.

with RA (Table 2). It was found that the levels of PS and t-PA were associated with the levels of TC, LDL-C and HDL-C and had no significant relationship with the levels of TG in the blood serum. They were 13-18% lower in patients with high TC, LDL-C, and low HDL-C levels than in those with normal levels of lipid metabolism markers. At the same time, the levels of hemostatic markers had virtually no relationship with serum TG concentration. The correlation analysis also did not reveal close relationships between the concentration of PC and t-PA with TG levels (r = -0.21 - 0.24), while indicators of the antithrombotic and fibrinolytic links of the hemostatic system were associated with the levels of TC, LDL-C and HDL-C (r = -0.25 - 0.31).

We found that the activity of the inflammatory process also significantly affected the severity of hemostatic disorders (Table 3). It turned out that as the disease activity increased, the average values of PC and t-PA significantly decreased and the proportion of patients with disorders in the antithrombotic and fibrinolytic links of the hemostatic system increased. Thus, in the group of patients with high levels (>75th percentile) of inflammatory markers CRP and ESR, the mean values of PC and t-PA were not only significantly 10% lower than those in the group of patients with minimal (≤25th percentile) activity, but also significantly lower compared with the group of patients with moderate inflammatory activity.

Similar patterns were found in the level of TNF-alpha and the total index of joint syndrome DAS28. Correlation analysis confirmed the relationship between hemostatic system parameters and disease

activity. The closest correlation (r = -0.32, r = -0.40) was recorded between the levels of TNF-alpha and CRP with the concentration of PC and t-PA, less close (r = -0.27, r = -0.30), but also significant with the value of ESR and the total DAS28 score. TNF-alpha can affect the expression of all major components of the fibrinolytic system.

Regarding the involvement of hemostatic disorders in the development of structural and functional changes in the cardiovascular system, it was found that in patients with RA, atherosclerotic changes in the vessels (decreased endothelium-dependent vasodilation of the brachial artery (EDVBA) in response to a reactive hyperemia test, thickening of the IMC CCA), as well as the intensity of atherosclerotic vascular lesions are closely associated with PC and t-PA deficiency; compared with the group of patients with normal levels, patients with reduced EDVBA and thickening of the IMC CCA were found 1.2 and 1.5 times more often (Table 4).

Serum levels of VWF in patients with RA showed a close relationship with disorders in the antithrombotic and fibrinolytic components of the hemostatic system. In particular, patients with PC and t-PA deficiency had significantly higher serum levels of VWF (by 19% and 12%, respectively) than patients with normal levels of PC and t-PA.

DISCUSSION

The results of the study revealed a deficiency of both PC and t-PA in patients with RA. Similar correlations of decreased levels of PC and t-PA in the blood were demonstrated in a study of infectious and septic conditions [11]. In the work of Mosnier, it was proved that the release of t-PA by endothelial cells is stimulated by PC [12]. Apoptosis inhibition and blockade of inflammation by activated PC were also found due to changes in the gene expression profile in endothelial cells.

This leads to a decrease in the formation of proinflammatory cytokines by activated monocytes, and protection of endothelial barrier function. Activated PC has an anti-inflammatory effect on endothelial cells and leukocytes. During inflammation, endothelial cells lose their antithrombotic properties due to the more intense expression of adhesive molecules, while the expression of nitric oxide and thrombomodulin, on the contrary, decreases [13]. In another study, the authors demonstrated that the levels of thrombin-activated fibrinolysis inhibitors were higher in conditions of increased inflammatory activity (CRP>10 mg/L) than in less severe inflammatory changes (CRP<10 mg/L) [14].

Inflammation leads to a shift in the balance of the hemostatic system towards a prothrombotic state. The PS system prevents thrombus formation by inhibiting the release of proinflammatory mediators and reducing vascular endothelial adhesion molecules [5]. This reduces leukocyte adhesion, tissue infiltration, and limits the focus of destruction of surrounding tissues, and reduces chemotaxis. Under conditions of inflammation, the above mechanisms are suppressed. K. Liang and co-authors [15] have established a link between the development of severe extra-articular manifestations of RA (including vasculitis) and the involvement of peripheral vessels in the process. A number of scientific studies have shown that inhibition of the reactions of activation of the PC causes a sharp increase in the production of IL-6, interleukin-8, TNF-alpha and other cytokines and reduces the body's tolerance to various endotoxins. Evidence has been obtained that PC not only blocks leukocyte activation but also regulates the activity of matrix metalloproteinases, which causes degradation of the extracellular matrix and localized ulceration [4, 13, 16]. It is in this pathogenetic plane that the mechanisms of pathogenic effects of TNF-alpha, IL-6, and a decrease in the concentration of PC and, accordingly, t-PA, which are destructive for both articular surfaces and the vascular wall, intersect.

The association of PC and t-PA deficiency with BMI confirms the multidirectional role of obesity in the formation of inflammation. White adipose tissue produces a number of peptides, including those that control fibrinolysis (plasminogen activator inhibitor-1). Changes in the volume of white adipose tissue in obesity lead to a disruption in the production of this signaling molecule. Adipocytes are able to produce plasminogen activator inhibitor-1, so in obesity, an increase in the production of this protein, respectively, reduces the level of t-PA. In addition, plasminogen activator inhibitor-1, which is synthesized in excessive amounts in obese individuals, stimulates the migration of macrophages, interleukin-8 (IL-8), and IL-6, i.e., proinflammatory cytokines [17]. In this situation, the role of obesity in the formation of inflammation is realized both directly, through the formation of TNF-alpha and IL-6, and indirectly through the stimulation of proinflammatory agents by plasminogen activator inhibitor-1.

PS deficiency was significantly more common in men with RA. This is associated with epidemiologic studies on the prevalence of systemic vascular manifestations, especially rheumatoid vasculitis, in the male population [18].

In other epidemiological studies, Weiler, 2011, demonstrated that in patients of older age groups, PC deficiency is 25-40% [19]. In our study, in this age group, there was only a tendency to increase the proportion of patients with coagulation disorders.

In terms of detailing the impact of dyslipidemia on the formation of vascular damage in patients with RA, an interesting result was obtained regarding the lack of correlation

between the levels of natural anticoagulants and their serum TG concentration. Obviously, this phenomenon is associated with the biochemical structure of TG, which does not contain phospholipids, unlike LDL-C and HDL-C. Although the role of antibodies to phospholipids in RA remains open today, a number of researchers describe cases of antiphospholipid syndrome in patients with RA [20-22]. Antiphospholipid antibodies have the ability to inhibit the PC system in several ways: through inhibition of thrombin formation, through the effect on thrombomodulin, through inhibition of the construction of PC complex proteins on the anionic surfaces of phospholipid matrices, and through inhibition of cofactors Va and VIIIa, etc. Antibodies to phospholipids also affect the levels of PC and/or protein S (acquired deficiency) [23].

The results obtained on the decrease in the level of natural anticoagulants logically fit into the general picture of endothelial dysfunction in patients with RA, since the deficiency of PC and t-PA initiate a cascade of biochemical changes, which, in turn, affect the development of structural and functional changes in the vessels, accelerating the development of the atherosclerotic process. The frequency of detection of atherosclerotic plaques in the CCA, as well as the severity of atherosclerotic vascular lesions according to the Wendelhag scale, were also higher in the group of patients with t-PA and PC deficiency.

CONCLUSIONS

1. Significantly more frequent deficiency of PC was found among men with RA, deficiency of both natural anticoagulants (PC and t-PA) - among patients with a BMI over 30, high serum levels of VWF, high levels of total cholesterol due to its atherogenic fractions and among patients with high intensity of atherosclerotic vascular lesions, but did not depend on the age group of patients and the duration of the disease.
2. Moderate strength of correlations between natural anticoagulants (PC and t-PA) deficiency, the degree of activity of the inflammatory process, TNF-alpha and the total index of the manifestation of the joint syndrome was revealed.
3. The study of PC and t-PA revealed a deficiency of important natural anticoagulants, which will expand the understanding of the mutually aggravating effect of the deficiency of these compounds and changes in known biologically active substances on the course of the disease, clinical heterogeneity of RA, and supplement the pathogenetic picture of RA with certain links. Compensation of PC deficiency may be a promising area of therapy aimed at restoring endothelial function, reducing the systemic inflammatory response, and inhibiting the atherosclerotic process in patients with RA.

REFERENCES

1. Steiner G, Verschueren P, Van Hoovels L et al. Classification of rheumatoid arthritis: is it time to revise the criteria? RMD Open. 2024;10(2):e003851. doi:10.1136/rmdopen-2023-003851.
2. Cush JJ. Rheumatoid Arthritis: Early Diagnosis and Treatment. Rheum Dis Clin North Am. 2022;48(2):537-547. doi:10.1016/j.rdc.2022.02.010.
3. Boissier MC, Semerano L. From coagulation to inflammation: novel avenues for treating rheumatoid arthritis with activated protein C. Rheumatology (Oxford). 2019;58(10):1710-1711. doi:10.1093/rheumatology/kez200.
4. Griffin JH, Zlokovic BV, Mosnier LO. Protein C anticoagulant and cytoprotective pathways. Int J Hematol. 2012;95(4):333-345. doi:10.1007/s12185-012-1059-0.
5. Oto J, Fernández-Pardo Á, Miralles M et al. Activated protein C assays: A review. Clin Chim Acta. 2020;502:227-232. doi:10.1016/j.cca.2019.11.005.
6. Aletaha D, Neogi T, Silman AJ et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569-2581. doi:10.1002/art.27584.
7. Matsuda R, Someya R, Kobayashi M et al. A quantitative assay system for protein C activity, the regulator of blood coagulation, based on a chromogenic method mimicking the blood coagulation cascade. Pract Lab Med. 2023;37:e00345. doi:10.1016/j.plabm.2023.e00345.
8. Cooper PC, Pavlova A, Moore GW et al. Recommendations for clinical laboratory testing for protein C deficiency, for the subcommittee on plasma coagulation inhibitors of the ISTH. J Thromb Haemost. 2020;18(2):271-277. doi:10.1111/jth.14667.
9. Roka-Moya YM, Zhernossekov DD, Kondratyuk AS et al. Rozrobka ta optymizatsiia metodiv vyznachennia aktyvnosti inhibitora aktyvatora plazminohenu 1-ho typu v plazmi krovi [Development and optimization of the methods for determiningactivity of plasminogen activator inhibitor-1 in plasma]. Ukr.Biochem.J. 2013;85(4):111-118. (Ukrainian)
10. Selvam V, Srinivasan S. Doppler-estimated Carotid and Brachial Artery Flow as Surrogate for Cardiac Output: Needs Further Validation. Indian J Crit Care Med. 2022;26(2):159-160. doi:10.5005/jp-journals-10071-24108.
11. Jenkins I. Evidence-based sepsis therapy: a hospitalist perspective. J Hosp Med. 2006;1(5):285-295. doi:10.1002/jhm.116.
12. Mosnier LO, Zlokovic BV, Griffin JH. The cytoprotective protein C pathway. Blood. 2007;109(8):3161-3172. doi:10.1182/blood-2006-09-003004.

13. O'Hehir ZD, Lynch T, O'Neill S et al. Endothelial Protein C Receptor and Its Impact on Rheumatic Disease. J Clin Med. 2024;13(7):2030. doi:10.3390/jcm13072030.
14. Bedeković D, Bošnjak I, Šarić S et al. Role of Inflammatory Cytokines in Rheumatoid Arthritis and Development of Atherosclerosis: A Review. Medicina (Kaunas). 2023;59(9):1550. doi:10.3390/medicina59091550.
15. Liang KP, Liang KV, Matteson EL et al. Incidence of noncardiac vascular disease in rheumatoid arthritis and relationship to extraarticular disease manifestations. Arthritis Rheum. 2006;54(2):642-648. doi:10.1002/art.21628.
16. Griffin JH, Zlokovic BV, Mosnier LO. Activated protein C: biased for translation. Blood. 2015;125(19):2898-2907. doi:10.1182/blood-2015-02-355974.
17. Kim JW, Kim JH, Lee YJ. The Role of Adipokines in Tumor Progression and Its Association with Obesity. Biomedicines. 2024;12(1):97. doi:10.3390/biomedicines12010097.
18. Favalli EG, Biggioggero M, Crotti C et al. Sex and Management of Rheumatoid Arthritis. Clin Rev Allergy Immunol. 2019;56(3):333-345. doi:10.1007/s12016-018-8672-5.
19. Weiler H. Multiple receptor-mediated functions of activated protein C. Hamostaseologie. 2011;31(3):185-195. doi:10.5482/ha-1166.
20. Marziale A, Bettacchioli E, Picart G et al. Antiphospholipid autoantibody detection is important in all patients with systemic autoimmune diseases. J Autoimmun. 2020;115:102524. doi:10.1016/j.jaut.2020.102524.
21. Misra DP, Ahmed S, Goyal M et al. Venous Thromboembolism in the Inflammatory Rheumatic Diseases. Rheum Dis Clin North Am. 2023;49(1):97-127. doi:10.1016/j.rdc.2022.08.001.
22. Virupannavar S, Brandau A, Guggenheim C et al. Possible association of etanercept, venous thrombosis, and induction of antiphospholipid syndrome. Case Rep Rheumatol. 2014;2014:801072. doi:10.1155/2014/801072.
23. Pengo V. Interaction between Antiphospholipid Antibodies and Protein C Anticoagulant Pathway: A Narrative Review. Semin Thromb Hemost. 2022;48(8):971-977. doi:10.1055/s-0041-1742083.

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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