УДК 577.1: [616.72-002.77+616.13-004.6

DOI: https://doi.org/10.34287/MMT.1(48).2021.1

I. M. Fushtey, S. L. Podsevakhina, A. I. Palamarchuk, O. V. Tkachenko
State institution «Zaporozhye Medical Academy of Postgraduate Education of the Ministry of Health of Ukraine»
Zaporozhye, Ukraine

І. М. Фуштей, С. Л. Подсевахіна, О. І. Паламарчук, О. В. Ткаченко
Державний заклад «Запорізька медична академія післядипломної освіти МОЗ Украины»
Запоріжжя, Україна

FEATURES OF DYSLIPIDEMIA AND ITS INFLUENCE ON ENDOTHELIUM FUNCTIONAL STATE IN PATIENTS WITH RHEUMATOID ARTHRITIS AND ARTERIAL HYPERTENSION

Особливості дисліпідемії та її вплив на функціональний стан ендотелію у пацієнтів з ревматоїдним артритом та артеріальною гіпертензією

Abstract

Purpose of the study. *Was to identify the features of blood lipid spectrum and endothelium functional state in patients with rheumatoid arthritis (RA) and arterial hypertension (AH).*

Materials and methods. *83 patients were examined (40 with RA combined with AH, 23 with RA and 20 with AH). The blood lipid spectrum and endothelial function were studied in all patients.*

Results. *The analysis of blood serum lipid parameters demonstrated that in patients with RA, regardless of the presence of AH, there was a significant increase of proatherogenic lipid profile parameters in comparison with those in healthy subjects.*

It was shown, that lower concentrations of high-density lipoproteins and higher atherogenic coefficient indices was a characteristic feature of the lipid profile in RA patients both with and without AH - in contrast to the same parameters of the lipid spectrum in patients with AH without RA. In the groups of patients with RA a significant increase of the brachial artery diameter at rest and decreased indices of endothelium-dependent vasodilation and endothelium-independent vasodilation were revealed. Subjects with RA in combination with AH had significantly lower indices according to the tests with both reactive hyperemia and nitroglycerin, while in patients with RA without AH, only NG-test was significantly lower.

Conclusion. *Dyslipidemia of atherogenic type and endothelial dysfunction develops at the initial*

Реферат

Мета дослідження. *Виявити особливості ліпідного спектра крові і функціонального стану ендотелію у хворих на ревматоїдний артрит (РА) та артеріальною гіпертензією (АГ).*

Матеріали та методи. *Обстежено 83 пацієнти (40 з РА у поєднанні з АГ, 23 з РА та 20 з АГ). У всіх хворих вивчали ліпідний спектр крові та функцію ендотелію.*

Результати. *Аналіз ліпідних параметрів сироватки крові показав, що у хворих на РА, незалежно від наявності АГ, відзначено достовірне збільшення концентрації проатерогенних показників ліпідограми в порівнянні з аналогічними показниками здорових осіб. Особливістю ліпідограми у хворих на РА як із наявністю АГ, так і без неї, є більш низькі концентрації ліпопротеїдів високої щільності і більш високі показники коефіцієнту атерогенності на відміну від аналогічних параметрів ліпідного спектру у хворих на АГ без РА. У групах хворих на РА відзначено достовірне збільшення діаметру плечової артерії у спокої і зменшення показників ендотелій залежної вазодилятації і ендотелій незалежної вазодилятації у порівнянні з групою контролю. При порівнянні досліджуваних параметрів у хворих на АГ без РА з хворими на РА відзначено, що пацієнти з РА в поєднанні з АГ мали достовірно нижчі показники при проведенні проб як з реактивною гіперемією, так і з нітрогліцерином, в той час як у хворих на РА без АГ достовірно нижче був тільки показник в пробі з НГ.*

stages of rheumatoid process and depends on the activity of the inflammatory process, the presence of extra-articular manifestations and rheumatoid factor seropositivity.

Keywords: *rheumatoid arthritis, arterial hypertension, dyslipidemia, endothelial dysfunction.*

Висновки. *Дисліпідемія по атерогенному типу і дисфункція ендотелію розвиваються на початкових етапах формування ревматоїдного процесу і залежать від активності запального процесу, наявності позасуглобових проявів, серопозитивності за ревматоїдним фактором.*

Ключові слова: *ревматоїдний артрит, артеріальна гіпертензія, дисліпідемія, дисфункція ендотелію.*

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune rheumatic disease, which is the most common and severe in cohort of all joints inflammatory diseases, the incidence of which in the population ranges from 0,6 to 1,3% [1]. Now it has been proven that the main reason of premature mortality in RA (approximately 40–50%) are diseases of the cardiovascular system caused by atherosclerotic vascular lesions, which develops for 10 years earlier than in the general population. It is assumed that the atherosclerosis accelerated development is actually a kind of extra-articular manifestation of RA [2]. The standardized mortality rate from cardiovascular accidents (myocardial infarction, stroke, sudden coronary death) appears 1,5 times higher in RA than in the general population [3].

To date, it has been proven that arterial hypertension (AH) is the most important modifiable risk factor not only in the general population, but in RA patients too. The presence of AH 3–6 times increases the risk of cardiovascular complications in RA. The incidence of AH in RA is on average 50% higher than in the general population. There is early development of isolated systolic hypertension in patients with RA which is the most unfavorable with respect to the cardiovascular complications incidence. There are following possible reasons for increased blood pressure (BP) in RA: the presence of chronic inflammation and autoimmune disorders that forms the basis of disease pathogenesis, metabolic disorders, hypodynamia, genetic factors and the use of antirheumatic drugs with potentially hypertensive effects. It has been shown that in about 56% of subjects with RA without signs of cardiovascular pathology, systolic blood pressure exceeds 140 mmHg and in a study conducted with the participation of 400 patients with RA, the presence of hypertension was revealed in 70,5% of patients. It is a characteristic that hypertension in persons with RA is highly resistant to therapy, and of 60,6% of patients who were on antihypertensive therapy, optimal blood pressure control was achieved only in 22% [4]. The significance of hypertension in the proatherogenic effect of RA was also shown in a study of 75 patients with RA, 15 of whom (21%) had coronary atherosclerosis. At the same time, patients with a combination of RA and atherosclerosis were characterized by a significantly higher prevalence of AH (46,7% and 14,5%, respectively) [5]. The reasons for atherosclerosis development and its accelerated progression in patients with RA are not fully clear. It has been shown that the pathogenesis of these processes in RA is determined not only by traditional risk factors such as dyslipidemia, diabetes mellitus, AH, increased body mass index, reduced physical activity, but also by the presence of specific factors – primarily high grade chronic systemic inflammation [6]. A number of studies showed that an increased risk of cardiovascular pathology in RA is associated with the presence of dyslipidemia, but at the same time, it has a special character, typical for the acute phase of the inflammatory response [7].

Impaired endothelial function is one of the most important mechanism of cardiovascular pathology development in RA patients. The endothelial dysfunction (ED) arises as a result of systemic inflammation even in the absence of traditional atherogenesis factors and significantly affects the risk of atherosclerosis development and progression [8]. Recently, in numerous studies, ED has been discussed as an etiological factor for blood pressure increasing and acts as one of the hypertension pathogenesis component [5].

The literature pooled data suggests that atherosclerosis is not so much a pathology accompanying RA as a concomitant process of cardiovascular system damage. However, the lack of an unambiguous understanding of the cardiovascular system state in various clinical variants of RA, both with and without hypertension, hinders the development of adequate methods for the prevention of cardiovascular complications and determined the necessity of present study.

The goal of the study was to identify the features of blood lipid spectrum and endothelium functional state in patients with RA and arterial hypertension AH.

MATERIALS AND METHODS

In order to realize the goal of the study, 83 patients were examined on the basis of

cardiorheumatological department of Municipal Uncommercial Institution «City Hospital № 10» of Zaporizhzhia City Council. All patients signed appropriate informed consent form for study participation. The mean age of the patients was (51,6 ± 5,1) years; there were 19 men (23,1%) and 64 women (76,9%). Such women predomination ratio (1 : 3) corresponds to the literature data on sexual dimorphism in patients with RA [7]. The following groups were formed: Group 1 – 40 patients with RA and AH, Group 2 – 23 patients with RA without AH, and Group 3 – 20 patients with essential AH. The diagnosis of RA was established according to the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) (2010) classification criteria. The diagnosis of arterial hypertension was established according to the recommendation of the European Society of Cardiology 2013 and the order of the Ministry of Health of Ukraine № 384, May 24, 2012. The mean duration of arterial hypertension was (5,05 ± 2,7) years, the average duration of RA was (9,5 ± 3,2) years. There were following prevalence: seropositive in clinical and immunological characteristics of RA (74,4% of patients), systemic manifestations (71,8%), 2nd degree of activity (53,8%), II-III radiological stages (79,5%), I–II degree of functional joint failure (71,8%). The control group consisted of 30 healthy volunteers with normal blood pressure and without diabetes mellitus, musculoskeletal system diseases and cardiovascular system pathology. All groups of patients were matched for age and sex.

Along with the generally accepted research methods, the blood lipid spectrum and endothelial function were studied in all patients. Analysis of total cholesterol (TC), high density lipoprotein cholesterol (HDL cholesterol) and triglycerides (TG) was performed by means of standard enzymatic method using test systems «Roche Diagnostics», Switzerland. Low density lipoprotein cholesterol (LDL cholesterol) was calculated using the Friedewald W. T. formula: LDL = (TC – TG/2,2) – HDL-cholesterol. The atherogenic coefficient (AC) was calculated using the A. N. Klimov's (1995) formula: AC = (TC – HDL-cholesterol)/HDL-cholesterol. Endothelium functional state was assessed by means of ultrasound method for determining of the endothelial-dependent flow-mediated brachial artery (BA) vasodilatation during the test with blood flow mechanical stimulation according to the recommendations set out in the Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilatation of the brachial artery (2002). Statistical analysis of the obtained data was processed using the PSPP software (version 1.0.1, GNUProject, 1988–2017). During the analysis, we used the methods of parametric and nonparametric variation statistics. The variant distribution character was determined by the Kolmogorov-Smirnov criterion. To describe normal distribution data of the sample the mean value of the parameter (M), standard error (m), and confidence coefficient (p) were used. The results were considered significant if the error probability was $p < 0,05$. Relationship between the parameters was studied by Spearman's rank correlation method.

Research results and their discussion. In patients with RA, hypertension at the time of examination was controlled. At the same time, the frequency of hypertension incidence increased with age: in patients of the age group 20–40 years, the percentage of hypertension was 24,36%, in patients of the age group 40–60 years old – 67,95%. In the majority of patients (88,46%), AH developed against the background of RA. In the first two years from the moment of diagnosed RA, AH was established in 21,79%. The average duration of AH, which was formed against the background of RA, was (5,83 ± 2,35) years. 19 (48%) patients had grade I of AH, 21 (52%) – grade II. The presence of arterial hypertension was significantly associated with the presence of extra-articular manifestations, in particular Raynaud's syndrome ($r = 0,61$, $p < 0,05$), as well as with RF ($r = 0,37$, $p < 0,05$) and activity according to the DAS scale ($r = 0,23$, $p < 0,05$). 96,12% of RA patients with AH received standardized RA therapy, of which the percentage of patients taking methotrexate at doses from 7,5 to 20 mg per week in combination with folic acid was 92,11%. 89,74% of patients received NSAIDs. Also, we revealed a high percentage (69,23%) of RA patients with AH who received for a long time (more than 4 months). GCS in doses from 2,5 mg to 20 mg. 33,33% of RA patients with arterial hypertension had clinical signs of CHF.

Analysis of lipid parameters of blood serum showed that in patients with RA, regardless of the presence of arterial hypertension, there was a significant increase of parameters of the proatherogenic lipid profile (TC, TG, LDL-C, AC) compared with similar one of healthy individuals (Table 1). A specific feature of the lipid profile in RA patients with and without AH was lower HDL-C concentration and higher AC values, in contrast to similar parameters of the lipid spectrum in AH patients without RA. There was a significant direct correlation between the level of TG, AC and the stage of AH ($r = 0,31$, $p = 0,04$ and $r = 0,40$, $p = 0,01$, respectively). In patients with RA in combination with AH, In the same group, TC, LDL-C and AC parameters depended on the activity of rheumatoid inflammation ($r = 0,42$, $p = 0,01$ and $r = 0,53$, $p = 0,00$ and $r = 0,45$, $p = 0,05$ respectively). Direct correlations were established between the concentrations of TC, AC and C-reactive protein in blood serum ($r = 0,45$, $p = 0,01$ and $r = 0,47$, $p = 0,01$, respectively).

Table 1

Characteristics of the lipid spectrum of blood serum depending on the presence of RA and AH

Groups	TC, mmol/l	LDL-C mmol/l	HDL-C, mmol/l	TG, mmol/l	AC, mmol/l
RA + AH, n = 40	5,0 ± 0,2*	3,2 ± 0,2*	1,1 ± 0,1*	1,5 ± 0,1*	3,1 ± 0,2*
RA, n = 23	5,1 ± 0,2*	3,2 ± 0,1*	1,1 ± 0,1*	1,5 ± 0,1*	3,7 ± 0,3*
AH, n = 20	5,1 ± 0,1*	2,9 ± 0,1*	1,5 ± 0,1*	1,5 ± 0,1*	2,4 ± 0,6
Control Group, n = 30	4,1 ± 0,1	2,4 ± 0,1	1,3 ± 0,02	1,0 ± 0,02	2,4 ± 0,1

Note: ** – $p < 0,05$ difference significance with the control group*

In RA patients without AH, we revealed significant medium strength inverse correlation between AC and RA duration ($r = -0,42$, $p = 0,02$) and a medium strength significant direct correlation between HDL-C and RA duration ($r = 0,27$, $p = 0,03$). Also, there was an inverse significant correlation of medium strength between the level of HDL-C and the form of RA ($r = -0,36$, $p = 0,04$) and a similar relationship between the concentration of TC and the X-ray stage ($r = -0,39$, $p = 0,03$).

Thus, traditional risk factors plays a role which is no less in atherogenesis in RA than inflammation [6]. According to a number of major researchers puublications, the absence of regular changes in the level of cholesterol and triglycerides in the blood during the development of cardiovascular manifestations is not a reflection of the reduced role of lipid disorders in the pathogenesis of atherosclerosis in RA, but indicates only their special nature. The lipid profile in subjects with RA is usually described as proatherogenic and its characteristic feature is not so much increased LDL levels, but rather qualitative changes in their structure. This is manifested, first of all, by the presence of small density particles, which refletct the proatherogenic nature of changes in the lipid profile and it is combined with a 7-fold increase in the risk of coronary artery disease and MI. Such changes, usually, develops in parallel with a decrease in the content of HDL-cholesterol and an increase in the ratio of LDL-cholesterol/HDL-cholesterol [10]. Thus, the presence of preclinical atherosclerosis in patients with RA, manifested by a significant increase in carotid arteries of the intima-media thickness and the frequency of detection of plaques in it are combined with the presence of intense systemic inflammation and increased plasma concentration of CRP, ICAM-1, VCAM-1, IL-6 and TNF-α, and lipid metabolism disorders with an increased levels of plasma TG and a decreased one of HDL-cholesterol. Multivariate regression analysis established a relationship between IMT, CRP, the presence of plaques, and plasma apoB levels [3].

As it follows from the Table 2, in both selected groups of RA patients there was a significant increase in the diameter of the brachial artery at rest and decreased parameters of endothelium-dependent (EDVD) and endothelium-independent vasodilation (ENVD) compared with the control group. EDVD and ENVD parameters in the group of patients with arterial hypertension without RA were also significantly lower in comparison with those parameters of healthy persons. When comparing the studied parameters of patients with AH without RA and the same one in patients with RA alone, it was found that patients with RA in combination with AH had significantly lower probe parameters of both reactive hyperemia (RH) and with nitroglycerin test (NG), while in patients with RA without AH, only the parameter in the test with NG was significantly lower. So, the groups of examined patients can be divided according to the severity of disorders of the vasoregulatory function of the endothelium: AH, RA without AH, RA in combination with AH.

Table 2

Endothelial function parameters depending on the presence of RA and AH

Parameter	RA + AH, n = 40	RA, n = 23	AH, n = 20	Control group, n = 30
Initial flow velocity, m/s	0,58 ± 0,16*	0,57 ± 0,20*	0,70 ± 0,15	0,69 ± 0,16
Initial BA diameter, mm	3,9 ± 0,68*	4,0 ± 0,58*	3,60 ± 0,52	3,40 ± 0,6
Flow-dependent dilation at 60 sec, %	14,77 ± 8,36*	14,3 ± 12,08*	18,11 ± 11,9*	22,18 ± 4,88
NG-induced dilatation, %	18,04 ± 12,7**	19,7 ± 10,1**	20,6 ± 3,4**	25,3 ± 6,3
Reactive hyperemia, % of speed increasing	107,8 ± 29,5**	133,7 ± 22,8*	119,2 ± 22,1**	145,4 ± 42,4

Note: *Significance of parameters differences in comparison with the data of the control group: * – $p < 0,05–0,001$; ** – significance of differences between flow-dependent dilation and NG-induced dilatation in groups, $p < 0,05–0,001$*

In patients with RA in combination with AH, an inverse significant relationship between the EDVD parameter and ESR level ($r = -0,26$, $p = 0,03$) was revealed. In patients with RA without AH, an inverse significant correlation was obtained between EDVD and the form of RA ($r = -0,33$, $p = 0,04$), ESR level ($r = -0,26$, $p = 0,03$). ENVD was also correlated with the ESR parameter ($r = 0,11$, $p = 0,04$).

According to the literature data, one of the most important mechanisms of cardiovascular pathology development in RA and its main prognostic signs is endothelial dysfunction, which is a result of systemic inflammation even in the absence of atherogenesis traditional factors and significantly affects atherosclerosis development and progression risks [11]. Thus, in a study of young patients with RA and low disease activity, it was shown that the intensity of endothelium-dependent relaxation was reduced from 5,7 to 3,2%, while regular treatment for 1 year was accompanied by its significant normalization [12].

In accordance with the results of a number of modern clinical trials, the nature of vascular damage in RA has significant features. In contrast to the traditional course of atherosclerosis with a predominant damage of the aorta and large arteries, RA resulted a diffuse damage of the arterial system with clear functional signs of arteriosclerosis and involvement of microcirculation vessels. [13]. In the clinical study of 66 patients with RA, systemic inflammation, which was characterized by an increase in the CRP level and an increase in ESR, was combined with signs of generalized endothelial damage and an increased plasma levels of von Willebrand factor. Under these conditions disturbances of microvessels functional state was manifested by the abnormal nature of their endothelium-independent relaxation, the intensity of which has inverse correlation with CRP level. 4-week anti-inflammatory therapy resulted decreasing of CRP levels, but not normalization of vascular function [14].

CONCLUSIONS

1. There were significantly more expressed lipid spectrum disturbances (decrease in HDL-C and an increase of AC) in patients with rheumatoid arthritis in combination with arterial hypertension and in patients with rheumatoid arthritis without arterial hypertension comparing with those, who have hypertension without rheumatoid arthritis. At the same time, in patients with rheumatoid arthritis without arterial hypertension, there were more expressed decreasing in HDL-C and an increasing in AC compared with patients with rheumatoid arthritis in combination with arterial hypertension.

2. Dyslipidemia of atherogenic type develops at the initial stages of the formation of the rheumatoid process and depends on the activity of the inflammatory process, presence of extra-articular manifestations and rheumatoid factor seropositivity.

3. There is a more significant impairment of endothelial function in patients with rheumatoid arthritis in combination with arterial hypertension compared with patients with rheumatoid arthritis without arterial hypertension and arterial hypertension without rheumatoid arthritis.

4. Dysfunction of the endothelium revealed already in the early stages of rheumatoid inflammation process and is associated with extra-articular manifestations, the presence of rheumatoid factor and the activity of the pathological process.

Authors disclaims any conflict of interests and the existence of finance.

REFERENCES

1. Mueller RB, Kaegi T, Haile SR et al. Disease Characteristics and Rheumatoid Arthritis Development in Patients with Early Undifferentiated Arthritis: A 2-year Followup Study. J.RMD Open. 2018 Jun 6; 4 (1): e000673. doi: 10.1136/rmdopen-2018–000673.

2. Del Rincon I. Atherosclerosis in rheumatoid arthritis: what to look for in studies using carotid ultrasound. J. Rheumatol. 2010; 37: 890–893 https://doi.org/10.3899/jrheum.100183.

3. Trukhan DI., Ivanova DS, Belus KD. Rheumatoid arthritis: influence of inflammation and anti-inflammatory therapy on cardiovascular risk factors. Meditsinskiy sovet = Medical Council. 2020;(11):32–44. https://doi.org/10.21518/2079-701X-2020-11-32-44.

4. Bazina IB, Kozyrev OA, Pavlolva MV et al. A comorbid patient: rheumatoid arthritis and hypertension. Vrach. 2020; (3): 28–32. DOI: org/10.29296/25877305-2020-03-05.

5. Gromova MA, Myasoedova S E. Arterial hypertension, cardio-vascular system and pain characteristics of patients with rheumatoid arthritis. Fundamental research. 2014; 10 (4): 651–653. http://fundamental-research.ru/ru/article/view?id=35597.

6. Ferreira HB, Melo T, Paiva A, Domingues MDR. Insights in the Role of Lipids, Oxidative Stress and Inflammation in Rheumatoid Arthritis Unveiled by New Trends in Lipidomic Investigations. Antioxidants (Basel). 2021; Jan 2;10 (1): 45. DOI: 10.3390/antiox10010045

7. Starodubova Yu, Osipova IV. Characteristics of Dyslipidemia and the duration of rheumatoid

arthritis in women. Ateroscleroz. 2017; 13 (3): 33–42. https://ateroskleroz.elpub.ru/jour/article/view/51/51.

8. Yang X, Chang Y, Wei W. Endothelial Dysfunction and Inflammation: Immunity in Rheumatoid Arthritis. Mediators Inflamm. 2016; https://doi.org/10.1155/2016/6813016.

9. Ferraz-Amaro I, Winchester R, Gregersen PK. Coronary Artery Calcification and Rheumatoid Arthritis: Lack of Relationship to Risk Alleles for Coronary Artery Disease in the General Population. Arthritis Rheumatol. 2017; 69 (3): 529–541. doi: 10.1002/art.39862.

10. Ikdahl E, Rollefstad S, Wibetoe G.et al. Predictive Value of Arterial Stiffness and Subclinical Carotid Atherosclerosis for Cardiovascular Disease in Patients with Rheumatoid Arthritis. J. Rheumatol. 2016; 43 (9): 1622–1630. DOI: 10.3899/jrheum.160053.

11. Idris-Khodja N, Ouerd S, Trindade M et al. Vascular smooth muscle cell peroxisome proliferator-activated receptor γ protects against endothelin-1-induced oxidative stress and inflammation. J. Hypertens. 2017; 35 (7): 1390–1401. DOI: 10.1097/HJH.0000000000001324.

12. Knyazeva AK, Komarova EB, Bludova NG. Endothelial dysfunction in patients with rheumatoid arthritis and comorbidity. Modern Rheumatology Journal. 2017; 11 (4): 25–29. https://doi.org/10.14412/1996-7012-2017-4-25-29.

13. Aleksandrova LA, Subbotina TF, Filipova NA et al. The relationship of endothelial factors of vasoregulation and the state of the antioxidant system with clinical manifestations of rheumatoid arthritis. Regional blood circulation and microcirculation. 2020; 19 (1): 60–66. DOI: 10.14739/2310-1210.2016.6.8548.

14. Yang Z, Shen Y, Oishi H et al. Restoring oxidant signaling suppresses pro-arthritogenic T-cell effector functions in rheumatoid arthritis. Sci Transl Med. 2016; 8 (331): 331–338. DOI:10.1126/scitranslmed.aad7151.

Стаття надійшла до редакції 01.03.2021