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COMBINATION OF HYPERTENSION AND RHEUMATOID ARTHRITIS: FEATURES OF THE LIPID PROFILE

Abstract. *The problem of the peculiarities of comorbid pathology has recently attracted more and more attention. The relevance of determining the features of the lipid profile in patients with arterial hypertension in combination with rheumatoid arthritis, especially given the insufficient control over the level of blood pressure, lies in the possibility of better control over the level of cardiovascular risk and more targeted prevention of severe cardiovascular events.*
Keywords: *lipids, hypertension, rheumatoid arthritis*

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by a high level of disability and a high frequency of comorbid diseases, especially cardiovascular diseases (CVD), which is associated with common pathogenesis. There is a link between autoimmune diseases and atherosclerotic diseases, especially in patients with RA. The pathogenesis of CVD development and it`s progression in RA patients includes common inflammatory mediators, posttranslational protein modifications and subsequent immune responses, as well as changes in lipoprotein composition and function, increased oxidative stress, and endothelial dysfunction [1]. Some traditional cardiovascular risk factors, such as smoking, diabetes, or high-density lipoproteins (HDL), are more common in RA patients and may increase CVD morbidity and mortality [2]. However, there is evidence that concentrations of total cholesterol (TC) and low-density lipoprotein (LDL) have not been associated with the progression of atherosclerosis among patients with RA [3]. On the other hand, it is possible to detect much lower concentrations of the lipids in relation to

the general population, especially with high disease activity in patients with RA [4]. The progression of atherosclerosis in RA is more significant with low and moderate activity even among patients on antirheumatic and hypolipidemic treatment. Moreover, the development of atherosclerosis in RA patients is determined by the levels of lipids, inflammatory and immune disorders [5].

The problem of arterial hypertension (H) and dyslipidemia in patients with RA began to attract more attention: out of 327 patients with RA (mean age 53 ± 11 years, 68% of women), about 37% had systolic blood pressure (SBP) > 140 mm Hg, statins were taken only 6%, antihypertensive drugs - 24%, and 68% of these patients did not reach the recommended target levels of BP and lipid levels [6]. Even in patients with newly diagnosed H, the level of TC can affect the response of BP to adrenergic stimulation, as well as the outcome of target organ damage: in people with higher levels of TC (0.54 +/- 0.07, 0.67 +/- 0.14, 0.68 +/- 0.15, P <0.05) significantly greater thickness of carotid artery intima-media complex is determined [7]. It was found, that residual cholesterol (RC) have the highest correlation with H among lipid profiles, including TC, HDL, LDL, and triglycerides (TG), with odds ratio 1.59 (95% confidence interval: 1.58-1.59). Moreover, an increase in TC levels may precede the development of H, which indicates the potential role of TC in the development of H [8].

Increased risk of RA, that is releted to CVD, is paradoxically associated with relatively low concentrations of TC, a phenomenon nemed "lipid paradox" linked to the presence of systemic inflammation [9], and the concentration of HDL with more rapid progression of atherosclerosis [3]. The study of Ferré et al. showed that HDL levels are the main determinant of vascular reactivity and antiatherogenic activity in people with medium and high risk of CVD [3, 10].

Patients with RA have lower survival rates than the general population due to the development of CVD, such as myocardial infarction and angina pectoris, which have been developed before the official diagnosis of RA. This is associated with a higher level of systemic inflammation (after adjusting for traditional factors) [11]. At the same time, 32.7% of patients with RA may have preclinical atherosclerosis [12-14], which justifies the need to prescribe not only basic antirheumatic treatment,

but also to take into account the consequences caused by both inflammation and other traditional risk factors for CVD.

Objective: To establish the frequency of dyslipidemia in patients with RA and resistant H (RH), RA and H, RA, H. To find out the frequency and features of lipid profile disorders in patients with RA and RH. Identify factors that affect lipid levels in patients with RA and RH. The null hypothesis was formed: in patients with RA and RH the frequency of dyslipidemia does not exceed the data of the general population.

Criteria for inclusion in the study: age from 45 to 74 years (middle and old age, according to the WHO classification, 1968); reliable diagnosis of RA and basic therapy according to ACR / EULAR criteria (2010, 2015); left ventricle ejection fractionore than 40%, K^+ serum level from 3.0 to 5.0 mmol / l.

Exclusion criteria: H 3 stage; secondary H; hypotension; severe arrhythmias and conduction abnormalyties; alcohol and drug addiction or mental disorders; oncological and hematological diseases; gout.

Materials and methods. 360 medical histories and outpatient cards were reviewed, from which 179 people were selected and examined. 4 groups were formed: 1 group - patients with RH and RA (n = 62), 2 group - patients with H and RA (n = 39), 3 group - patients with RA without H (n = 41), 4 group - patients with H without RA (n = 37). A survey of patients with RA and RH / H was conducted, which took into account the duration of both RA and H, specifying the duration and nature of basic therapy in both cases, especially the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticosteroids (GCs). A laboratory study was performed to determine the content of TC and it`s profile, creatinine, levels of rheumatoid factor, C-reactive protein (CRP); glomerular filtration rate (GFR) was calculated using the formula CKD-EPI, RA activity according to DAS28-CRP. Commission on Ethics at Bogomolets National Medical University agreed to conduct this study (protocol № 109 from Mar 01, 2018).

All study groups are comparable in age, sex, and level of smoking; groups of patients with RA are comparable in the RA type, duration of RA, as well as RA activity (the level of CRP and DAS28-CRP scale, which corresponded to high

disease activity in groups 1, 2 and 3), the need for GCs and NSAIDs use; groups of patients with H are comparable in duration of H (Table 1).

Table 1

Clinical characteristics of patients

	Group 1 (n=62)	Group 2 (n=39)	Group 3 (n=41)	Group 4 (n=37)
Age, years, M ± σ	62,9 ± 9,0	61,9 ± 7,0	59,1±8,5	60,6±9,6
Women, abs. (%)	52 (83,9)	30 (76,9)	37 (90,2)	31 (83,8)
Seropositive RA, n (%)	51 (82,3)	29 (74,4)	31 (75,6)	-
DAS28-CRP, M ± σ	5,4 ± 1,0	5,6 ± 1,0	5,3±1,1	-
Took NSAIDs, abs. (%)	50 (80,6)	33 (84,6)	31 (75,6)	-
Took GCs, abs. (%)	21 (33,9)	11 (28,2)	15 (36,6)	-
Duration of RA, years, M ± σ	9,2 ± 8,0	8,7 ± 7,1	8,6±9,2	-
Duration of H, years, M ± σ	10,8 ± 7,2	7,0 ± 3,8	-	9,2±6,1
Smoking, abs. (%)	7 (11,3)	5 (12,8)	7 (17,1)	5 (12,2)

Stratification of risk factors for CVD was made using two methods: Framingham scale (FS, 2008) and QRISK3 scale. Blood lipid spectrum was determined by the levels of TC, LDL, HDL and TG using test systems Cobas 6000, Roche Diagnostics (Switzerland). The level of very low density lipoprotein (VLDL) was calculated by Friedwald's formula:

$$VLDL = TG / 2.2 \qquad (1)$$

The atherogenic index (IA) was calculated as the ratio of the amount of cholesterol of proatherogenic lipoproteins to HDL according to the formula:

$$IA = TC - HDL / HDL \qquad (2)$$

IA was evaluated as normal at a value of ≤ 3.0 [15, 16]. The level of proatherogenic lipids (Non-HDL) and cholesterol ratio (TC\HDL) were determined.

Serum lipid levels were compared according to data from the European Atherosclerotic Society and the European Federation of Clinical Chemistry and Laboratory Medicine [15, 16].

Statistical processing was performed using "IBM SPSS Statistics. Version 22". Parametric statistical methods were used for descriptive statistics - the mean value

(M), standard deviation (σ), standard error (SE), 95% confidence interval (95% CI) were determined; the median values (Me), 25 and 75 quartiles (Q25 - Q75) as well as a percentage (%) were used. Comparison of groups was performed using Pearson's χ^2-test (corrected by Yates), Fisher's exact test. For the measurement of relationship between variables were used odds ratio (OR) and the Pearson correlation.

Results. As a result of the study of 10-year fatal risk of CVD, it is found that in patients of groups 1 and 2 the risk of CVD according to FS, 2008 is moderate (13.7 (8.6-21.5)% and 13.7 (10.0- 21.5)%) against low in groups 3 and 4 (respectively 3.3 (2.4-5.3)% and 9.6 (5.4-15.8)%, p <0.05), which is identical to the data of another smaller study [17]. According to QRISK3, the following results are obtained: moderate risk in patients of groups 1 and 2 (13.5 (7.9-22.3)% and 11.9 (8.8-19.0)%), against low in groups 3 and 4 (respectively 3.9 (2.1-7.8)% and 9.6 (5.4-15.8)%, p <0.05). In group 1 dyslipidemia (DL) is defined in 42 (67,7%) patients, the level of TC in comparison with group 4 is higher by 0,27 mmol / l, TG - by 0,22 mmol / l and HDL is lower by 1, 96 mmol / l, only TG is 0.21 mmol / l higher than in group 3 (all p <0.05). Analyzing the lipid spectrum of blood of patients with DL, we have found that 11 (26.2%) patients have elevated LDL levels, 6 (14.3%) - TG, 2 (4.8%) - Non-LDL and in 4 (9.5%) people - a decrease in HDL concentration. In group 2, the frequency (71.8%) and the spectrum of DL do not differ, but in group 3 with the prevalence of DL in 61.0% the level of TG twice less often are increased (8.0%, χ^2 = 4.3, p <0,05), in group 4 the frequency of DL detection is lower (18 (48.6%) patients χ^2 = 4.0, p <0.05) with 2-times elevation of TG and reduction of HDL (1 (5.3%) patients in both groups, respectively χ^2 = 3.9 and χ^2 = 7.4, p <0,05). In patients from group 3, the frequency of DL is 12.4% higher than in group 4 (χ^2 = 4.2, p <0.05), the concentration of HDL is 1.87 mmol / l lower (χ^2 = 8.2, p <0, 05).

Therefore, DL is diagnosed more often among patients with RA in combination with H than in patients with H without RA with prevalence of hypertriglyceridemia and decreased levels of antiatherogenic lipids. Adverse effects of RA on the degree of DL is not defined (Table 2).

Table 2

Parameters of the lipid profile in patients with Me (25% - 75%)

	Group 1 (n=62)	Group 2 (n=39)	Group 3 (n=41)	Group 4 (n=37)
TC, mmol \ l	5,47 (4,85-6,29)‡	5,30 (4,93-6,23)	5,31 (4,55-6,50)	5,20 (4,78-6,31)
TG, mmol \ l	1,23 (0,92-1,61)#‡	1,20 (1,00-1,56) #‡	1,02 (0,87-1,38)	1,01 (0,85-1,45)
LDL, mmol \ l	3,36 (2,98-4,17)	3,23 (2,27-4,03)	3,26 (2,62-4,16)	3,27 (2,78-3,96)
VLDL, mmol \ l	0,55 (0,41-0,73) #	0,54 (0,45-0,71) #	0,46 (0,39-0,62)	0,61 (1,49-0,92)
HDL, mmol \ l	1,41 (1,16-1,83)‡	1,42 (1,13-1,80) ‡	1,50 (1,15-4,16) ‡	3,37 (2,78-3,96)
TC\HDL	3,71 (3,07-4,65)‡	3,78 (2,78-4,59) ‡	3,73 (2,90-4,39)	4,11 (3,36-5,11)
Non-HDL, mmol \ l	1,98 (1,64-2,42)	1,98 (1,71-2,52)	1,96 (1,51-2,38)	1,98 (1,76-2,28)
IA	2,70 (2,07-3,65)‡	2,78 (1,78-3,59)	2,70 (1,89-3,39)	3,08 (2,25-4,12)

Notes: # - p <0.05 compared to group 3, ‡ - p <0.05 compared to group 4.

It is found that after increasing of the activity of RA (DAS28-CRP), patients with RA and RH have elevated levels of TC (r = 0.28, p <0.05), LDL (r = 0.29, p <0.05), TG (r = 0.30, p <0.05), and CHD / HDL (r = 0.29, p <0.05), decreased HDL level (r = -0.32, p <0.05). High levels of serum CRP are closely associated with the frequency of DL (OR = 1.12, 95% CI 1.04-1.19, p = 0.02), especially with a decrease of HDL (OR = 1.71, 95% CI). 1.12-2.14, p <0.001), but in patients with DAS28-CRP above 6.3 there was a decrease in the level of TC to 4.68 (4.20-6.29) mmol / l, HDL to 1,07 (0.89-1.21) mmol / l and an increase in TG to 1.74 (1.22-2.19) mmol / l. It is found a decreased LDL levels (2.89 (1.95-4.24) mmol / l against 3, 44 (3.16-4.17) mmol / l, p <0.01), TC (4.75 (1.13-2.07) mmol / l vs. 5.54 (4.96-6.4) mmol / l, p <0.05), TG (1.15 (0.9-1.53) mmol / l vs. 1.47 (1.13-2.07) mmol / l, p <0, 05), HDL (1.08 (1.02-1.25) mmol / l vs. 1.55 (1.25-1.9) mmol / l, p <0.05) and increased HDL / HDL 4.40 (3.32-5.22) vs. 3.58 (4.65-4.17), p <0.05) in patients with RA in combination with RH and increased CRP ≥ 25 mg / l, compared with patients with CRP <25 mg / l. Thus, the "lipid paradox" is exacerbated by the combination of RA with RH. This phenomenon has been confirmed and emphasized that despite the decrease in the level of proatherogenic lipids, atherosclerotic

changes are still progressing [18].

Patients with DAS28-CRP ≥6.3 and RA duration ≥8 years have three times the risk of developing fatal CVD (respectively OR = 2.71, 95% CI 1.18-3.21 and OR = 3.17.95% CI 2.14-3.65, both p <0.001), which corresponds to the data of other researchers who identified a 4-fold increase in CVD risk [17]. In the case of GCs use, the levels of TC (r = 0.28, p <0.05), LDL (r = 0.29, p <0.05) and TG (r = 0.30, p <0.05) increased, HDL level (r = -0.32, p <0 , 05) decreased; in the presence of visceral manifestations the levels of TC (r = 0.28, p <0.05), LDL (r = 0.29, p <0.05) and TG (r = 0.30, p < 0.05) are increased, the level of HDL (r = -0.32, p <0.05) decreased, which corresponds to a study of 1543 people with RA (mean age 54 ± 15 years, 71% of women) [19] .

Conclusions. The highest incidence of dyslipidemia in patients with RA in combination with RH (67.7%), associated with higher levels of proatherogenic lipid fractions (all p <0.05) with a statistically insignificant difference compared with patients with RA in combination with H, and RA. With increasing RA activity in patients, the levels of TC, LDL, TG and CKD / HDL are elevated (all p <0.05). The presence and high activity of RA have a significant proatherogenic effect in the studied cohort of patients.

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