LIPID PROFILE IN COMPREHENSIVE TREATMENT OF CARDIOVASCULAR EVENT OF PATIENTS WITH RHEUMATOID ARTHRITIS

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Currently, rheumatic diseases remain the most common pathology worldwide, particularly in Ukraine. Rheumatoid arthritis (RA) ranks first among them. This is the most common form of inflammatory joint disease, affecting about 1% of the population [1]. The state of chronic inflammation in patients with RA creates conditions for the hyperproduction of proinflammatory cytokines and the relative failure of the synthesis of anti-inflammatory mediators. The result of this imbalance is the development of atherosclerotic vascular disease, an early stage of which is indicated by the gain of thickness of the intima-media complex, the development of endothelial dysfunction (ECD), [2,4]. Hypertension (HT) in combination with RA is characterized by a high incidence of endothelial dysfunction and asymptomatic atherosclerotic disease of the major and peripheral vessels. (3)

Endothelial dysfunction, which determines adhesive and inflammatory changes, vasoreactivity and atheromatous plaque stability, has a direct effect on the progression of arterial hypertension and its sequela [5].

The development of endothelial dysfunction is associated with the influence of oxidative stress and impaired metabolism of homocysteine, which is accompanied by the secretion of a large number of proinflammatory mediators, an increase in procoagulant changes as well as local expression of matrix metalloproteinases, the production of powerful vasoconstrictive agents (endoperoxides, endothelin-1, angiotensin II, vascular endothelial growth factor), as well as cytokines and tumor necrosis factor-a, which inhibit the production of nitric oxide (No) and lead to damage and rupture of atheromatous plaque [6, 7] .

As vascular endothelial dysfunction plays a leading role in the development and destabilization of cardiovascular diseases, it is important to develop new approaches to the treatment of comorbid pathology [8,9]. One way to optimize the treatment of such patients is to add L-arginine, an essential amino acid that is a substrate for NOS, to basic therapy [10].

Thus, the issue of prevention of cardiovascular events, as well as the development of measures to improve the prognosis for already existing asymptomatic atherosclerosis in this category of patients is relevant [11]. Object:

To evaluate the effectiveness of oral use of L-arginine aspartate in the correction of endothelial dysfunction in patients with hypertension in combination with rheumatoid arthritis and to determine the effect of this therapy on the level of blood pressure and the spectrum of lipid profile.

Materials and mrthods. Case follow-up and treatment of 40 patients (including 38 women) aged 45–65 years (median - 54.03 ± 4.93 years) with I – II hypertension stage in combination with RA were performed. The mean duration of hypertension was 8.67 ± 4.61 years, for RA - 8.15 ± 4.23 years. The diagnosis of "Hypertension" was established in accordance with the recommendations of the Ukrainian Association of Cardiologists for the Prevention and Treatment of Arterial Hypertension 2018. The diagnosis of "Rheumatoid arthritis" was established according to the classification of the Association of Rheumatologists of Ukraine and diagnostic criteria of the American College of Rheumatologists (ACR / EULAR) 2010.

- The inclusion criteria are:
- age 40-65 years;

- occurrence of a verified diagnosis of HT of I – II stage, 1–2 grade ;
- occurrence of a verified diagnosis of RA;
- stable baseline therapy for RA (with duration of more then 6 months) and hypertension (≥ 1 month);
- reception of voluntary informed consent to participate in the study.
- The exclusion criteria are:
- age more than 65 years;
- established and verified diagnoses of ischemic heart disease, III stage hypertension and/or third grade hypertension, chronic heart failure of III-IV functional class;
- occurrence of cardiac arrhythmia, causing hemodynamic disorders;
- occurrence of acute disorders of cerebral circulation;
- chronic kidney failure (glomerular filtration rate (GFR) <60 ml/min /1.73 m2).

During the follow-up, all patients followed basic antihypertensive therapy using angiotensin-converting enzyme inhibitors (ACEI), sartans, calcium antagonists, diuretics, and lipid-lowering drugs, which did not change over the study period. 26 (65%) patients received RA methotrexate as basic therapy, the average dose of methotrexate was 12.13 ± 3.56 mg/week, the average duration of treatment was 5.06 ± 2.74 years. 14 (35%) patients received glucocorticoids, the average daily dose based on methylprednisolone at the time of the study was 6.05 ± 2.83 mg, and the average duration of treatment was 4.16 ± 2.52 years.

40 patients with arterial hypertension in combination with rheumatoid arthritis were examined. The patients are divided into two groups:

The first group (n = 20) were patients who received L-arginine aspartate in the form of oral solution of 15 ml, 2 times a day for 4 weeks in comprehensive treatment.

The second group (n = 20) were patients who were not prescribed L-arginine aspartate. The control group consisted of 20 practically healthy individuals, comparable by gender and age with major groups. (Table 1).

In the course of the study, all patients were determined by objective and subjective signs of hypertension and RA, anamnestic data were collected, physical, laboratory and clinical-instrumental examination at the beginning and end of the study (electrocardiography, self-monitoring of blood pressure, general clinical studies of blood, urine, biochemical blood test (creatinine, urea, lipid profile). Determination of GFR using the CKD-EPI formula (Chronic Kidney Disease Epidemiology Collaboration), daily monitoring of blood pressure was performed at the beginning of the study. The function of vascular endothelium was evaluated by the determination of the EDV by a standard technique (Celermajer D.S., 1997). The tolerability of the drug was evaluated on the basis of the subjective feelings of the patient, the evaluation of laboratory parameters, GFR, the frequency of development of adverse reactions. Statistical processing of the obtained data was performed using the licensed program STATISTICA 10. Mean values (M), standard deviation (Sd), standard error of the mean (m) were determined. To compare the indicators in the two independent groups, we used the Mann–Whitney U-test and Wilcoxon's test (W) to compare the two dependent groups. The degree of correlation between pairs of independent traits, expressed in a quantitative scale, was performed using the rank correlation coefficient r. Statistically significant differences in the study results were determined at $p < 0.05$.

Results. Under study of vascular endothelial function abnormalities of EDV in the initial state were noted in the majority of patients affected by hypertension in combination with RA - 39 (97.5%). No EDV abnormalities were detected in patients in the control group. The EDV parameter in patients with hypertension in combination with RA was significantly different from that of the control group ($p < 0.05$). In this case, vasoconstriction and lack of EDV dynamics in the sample with reactive hyperemia

were detected in 10 (25%) patients: paradoxical vasoconstriction (EDV <0) in 2 (5%) persons, lack of EDV dynamics parameters during the test with reactive hyperemia (EDV = 0) - in 5 (12.5%) patients. Decrease in EDV correlated with a decrease in GFR (r = 0.38; p = 0.015) and a level of SBP (r = 0.51; p = 0.02), DBP (r = 0.57; p = 0.01). Inclusion of L-arginine aspartate therapy in medication led to improvement of both subjective and objective parameters in the examined patients. According to the case follow-up, paradoxical vasoconstriction under the influence of treatment was stopped, normalization of endothelial function in the first group in all patients was achieved. Overall, in the group it was detected an improvement in EDV by 58.8% (p <0.05). In the second group, normalization of this parameter was found in 5 (41.7%) patients, in the whole group - by 24.1% (p <0.05). The use of L-arginine aspartate contributed to a significant improvement in endothelial vascular function with an increase in EDV by 53.7% in the first group compared with patients in the second group (p <0.05).

The levels of SBP and DBP in patients of the 1st and 2nd groups at the beginning of treatment did not differ significantly (Table 2). Analysis of the decrease in SBP and DBP levels at the end of the study in the groups showed its decrease by 35.8% and 37.2%, respectively (p <0.05) among the patients of the 1st group and by 28.7% and 26.4%, respectively (p <0.05) - among patients of the 2nd group 2. Thus, the addition of L-arginine aspartate to basic therapy resulted in a more significant decrease in SBP and DBP levels in patients of the first group. Positive dynamics of therapy were observed in all groups. No significant side effects were observed with the drug.

When studying the spectrum of lipid profile it was found that in the first group of patients who received L-arginine for 4 weeks in the comprehensive treatment, the level of total cholesterol (TC) was decreased by 10.7%, compared to the second group - 0.3%, where the level of total cholesterol remained virtually unchanged. Low density lipoproteins (LDLs) were decreased by 8.82% in the first group, and by only 0.2% in the second group. The level of triglycerides (TG) in the first group was decreased by 1.84% and by 0.6% in the second group, respectively. High density lipoproteins (HDL) were not change in the first group after treatment, in the second group it was decreased by only 0.8%, respectively.

Table 1.

Changes of parameters of endothelium-dependent vasodilation, pressure in patients with hypertension and RA under the influence of different treatment regimens

Parameter	The first group (n=20) (L-arginine)		The second group (n=20) (without L-arginine)		The control group n=20
	Before treatment	After treatment	Before treatment	After treatment	
EDV, %	8,8±1,7	11,8±1,5 (p<0,05)	8,5±1,2	9,7±1,2 (p<0,05)	12,6±2,9
SBP, mm of mercury	145,8±8,6	130,4±6,5 (p<0,05)	144,7±7,3	134,2±6,1 (p<0,05)	121,1±4,2
DBP, mm of mercury	88,5±1,5	76,1±1,4 (p<0,05)	87,7±1,4	84,5±1,7 (p>0,05)	73,5±1,6

* Statistical significance at the beginning and end of the study p <0.05

Table 2.

Dynamics of EDV parameters in patients with hypertension + RA

Parameter	The first group (n=20) (L-arginine)		The second group (n=20) (without L-arginine)	
	Before treatment	After 4 weeks	Before treatment	After 4 weeks
EDV in the normal condition	2 (10%)	9 (45%)	-	5 (25%)
Decreased EDV	16 (80%)	11 (55%)	14 (70%)	10 (50%)
Vasoconstriction	2 (10%)	without finding	7 (35%)	7 (35%)

* Statistical significance, p<0,05

Table 3.

Lipid profile parameters of the main group and the comparison group

Parameter	The first group (n=20) (L-arginine)		The second group (n=20) (without L-arginine)		The comparison group n=20
	Before treatment	After 4 weeks	Before treatment	After 4 weeks	
TC mmol/L	5,6±1,8	5,0*	5,56±1,5	5,54	5,51±1,2
LDLs	3,4±1,6	3,1±1,5*	3,35±1,2	3,34±164	3,21±1,7
HDL	1,24±1,4	1,25±1,4*	1,25±1,4	1,24±1,3	1,22±1,4
TG	1,63±1,6	1,61±1,2*	1,54±1,2	1,53±1,4	1,61±1,6

* Statistical significance, p<0,05

Results.

1. The use of L-arginine aspartate in the form of oral solution for 4 weeks in comprehensive treatment in patients with hypertension and RA led to a significant improvement in endothelial vascular function with an increase in the EDV in the first group compared with the patients in the second group (g <0.05), increasing the effectiveness of control of systolic and diastolic blood pressure.

2. The inclusion of L-arginine in comprehensive treatment of patients with hypertension and rheumatoid arthritis, is one of the ways of preventing dyslipidemia and cardiovascular events, as well as measures to improve the prognosis in the specified category of patients.

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