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Resveratrol more effectively than quercetin reduces endothelium degeneration and level of necrosis factor α in patients with coronary artery disease

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ABSTRACT

Introduction: endothelial dysfunction (ED) is one of the most important links in the pathogenesis of atherosclerosis (ASVD) — morphological basis of coronary artery disease (CAD).

Objective: to study the effect of polyphenolic antioxidants, resveratrol and quercetin, on endothelial degeneration factors in CAD patients.

Materials and Methods: the study involved 93 patients with coronary artery disease: stable angina pectoris, FC II. The *cytofluorometric technique* was applied to define the level of circulating endothelial microparticles (EMP) CD32⁺CD40⁺ in peripheral blood in order to identify ED. The content of tumor necrosis factor α (TNF- α), fibrinogen, hemocoagulation and lipid profile parameters were being determined in the blood, as well. Patients were divided into 3 groups. Basic therapy (β -blockers, statins, aspirin) was prescribed to 33 persons of the comparison group, patients of the study group 1 (30 persons) additionally received resveratrol at a dose of 100 mg daily, patients of the study group 2 (30 persons) got quercetin at a dose of 3 g per day. In 2 months, the second examination of the patients was performed in the amount indicated.

Results: under the influence of resveratrol a significant reduction of the level of TNF- α and the number of EMP in peripheral blood was shown, in contrast to the results of other study groups. All groups showed a decrease in total cholesterol and low-density lipoprotein cholesterol, statistical differences between data of groups were not found. Indicators of coagulogramma in all study groups did not change significantly, however, there was a statistically significant reduction of fibrinogen in the blood.

Conclusions: resveratrol, unlike quercetin, has a positive effect on the endothelial function and systemic inflammation, which may be the result of its influence on intracellular molecular cascades associated with the nuclear transcription factor of NF- κ B.

Key words: coronary artery disease, endothelial dysfunction, resveratrol, quercetin, circulating endothelial microparticles.

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INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality in Ukraine (67.3%), with dominating coronary heart disease (68.8%). Coronary artery disease (CAD) tops the list of 10 leading causes of death globally (12.8%) [1]. Morphological basis of CAD is atherosclerosis (ASVD), in particular, of the coronary arteries. Endothelial dysfunction (ED) is one of the most important links in the pathogenesis of atherosclerosis (ASVD) [2].

Violation of vasomotor, hemostatic, adhesive, angiogenic properties of the endothelium (ET) is the result of direct or indirect damage to cell membranes by free radicals, the oxidation-modified low-density lipoproteins (LDL), antigenic complexes, monocytes, macrophages, cytokines (CK), which leads to activation of endotheliocytes with possible subsequent apoptosis [3]. Prolonged exposure to activating factors contributes to the formation of a persistent imbalance of all endothelium-dependent functions. Chronic inflammation of low intensity, which is the pathogenetic basis of ASVD, supports ED. Thus ET, in turn, having a potent paracrine function, mediates and implements proinflammatory reaction, making a vicious cycle of vascular lesions' formation [4]. Proceeding from the above,

the search for effective correctors of ED, both of preventive and therapeutic action, is a perspective direction of modern medicine [5].

Our attention has been attracted by stilbene phytoalexin, resveratrol. Resveratrol is a polyphenol representative, it contains 2 aromatic rings and 3 reactive hydroxyl groups that contribute to its antioxidant activity. Resveratrol is found in more than 30 species of plants, providing protection from the damaging action of bacteria, viruses, ultraviolet exposure [6]. Molecular targets of resveratrol are nuclear factor kappa-B (NF- κ B), sirtuin-1 (SIRT-1), NO, sNOS/eNOS, adenosine receptors, free radicals, adhesion molecules ICAM, VCAM, E-selectin, MAP-kinase and many others [7, 8, 9]. It is flavonoid quercetin that has similar chemical structure and is well studied and having demonstrated the protective properties in acute coronary syndrome [10, 11].



The aim of our study was to investigate the effect of resveratrol compared with quercetin on the ED indicators, systemic inflammation, lipid blood profile and hemocoagulation in patients with stable coronary artery disease.

MATERIAL AND METHODS

The research involved 113 people. The study group included 93 patients (26 females and 18 males), aged 48 to 72, with the diagnosis of CAD: stable angina pectoris, FC II, CH 0-I, the average risk. Exclusion criteria were Stage 2 hypertension, rheumatic diseases, diabetes mellitus, chronic liver disease and kidney failure. The control group consisted of 20 healthy individuals. Every patient gave a written informed consent to participate in the research, according to the requirements of the Declaration of Helsinki. CAD diagnosis was confirmed clinically, by the data of cardiac stress testing and echocardiography (echo). Treadmill ergometer was used with a continuously increasing step-by-step protocol of dosed physical load with duration of one stage of 2 minutes. The test was considered to be "positive" in the case of occurrence of objective evidence of myocardial ischemia during the trial, functional class (FC) of CAD was determined by performing the declared load capacity, every patient completed a load capacity of 75 W, which corresponded to FC II. Using echo, central hemodynamics was being studied to identify systolic and diastolic dysfunction of the left ventricle (LV). Patients of the study groups had a saved ejection fraction (EF) of LV or its slight decrease (45-50%). All the patients showed signs of diastolic dysfunction by the type of violation of relaxation (type 1). In the presence of clinical symptoms (shortness of breath with exertion, palpitations, fatigue) and decrease in LVEF in the specified range, the diagnosis of heart failure (HF) with preserved systolic function (52% of patients with CAD) was established. The degree of risk was determined by the total assessment using SCORE table that was less than 2.3% of 10-year risk of mortality, and the values of LVEF, which corresponded to less than 3% of annual mortality risk. Therefore, the average risk for every patient of the study groups was established [12]. Standard therapy for coronary artery disease patients, together with recommendations for lifestyle (diet therapy, dosed physical exertion, smoking cessation), was prescribed; medications were also used: beta-blockers (5 mg of bisoprolol once a day in the morning), statins (10 mg of atorvastatin once a day at bedtime), 75 mg of aspirin at bedtime. After stabilization of the clinical course of CAD in a month after the start of the base treatment, resveratrol at a dose of 100 mg per day in one portion per os was additionally administered to patients of the study group 1, patients of the study group 2 were prescribed quercetin at a dose of 3 g per day per os. Before therapy with resveratrol and quercetin and after 2 months of starting treatment, clinical laboratory tests were conducted to patients.

For objectification of patients' condition before and after treatment an EQ-5D quality of life questionnaire with the expectation of EQ-5D index and parallel identification of the data on a visual analog scale EQ-5D-VAS was used. As a marker of ET damage, circulating in the bloodstream endothelial microparticles, formed as a result of apoptosis or activation of endothelial proinflammatory agents, were being studied. Determination of circulating endothelial microparticles (EMP) was made by identifying the expression of endothelial cell antigens CD32 and CD40 with monoclonal antibodies by flow *cytofluorometry* [13]. To assess the severity of chronic systemic inflammation, the concentration of tumor necrosis factor (TNF- α) in blood serum was determined by immunoassay and the concentration of fibrinogen

in the blood — by gravimetric methods. Hemocoagulation indicators were being studied as well: prothrombin time index (PTI), activated partial thromboplastin time (aPTT), international normalized ratio (INR). The content of total cholesterol, LDL cholesterol and high-density lipoprotein (HDL) were evaluated by photometric method.

Statistical analysis of the results of the research was carried out using BioStat and KyPlot programs. The hypothesis of normal distribution was checked by Shapiro – Wilk test. When comparing these study groups before and after treatment, paired Student's t-test was used, for inappropriate distribution — Wilcoxon signed-rank test and Fisher's exact test. When comparing data between groups, unpaired Student's t-test and Steel – Dwass test (nonparametric analogue of Tukey's range test) or Wicocson test were used. Search for relations between variables was held using Pearson's correlation or, subject to maldistribution, using Spearman's and Kendall's rank correlation. Data differences were considered to be significant at a level of $p < 0.05$.

RESULTS

The mean EQ-5D-index score before treatment in patients with coronary artery disease was 0.741 ± 0.066 , EQ-5D-VAS – 53.63 ± 5.14 . Patients taking resveratrol, most often, compared with those of other groups, noted the boost of energy, increased working capacity, reducing the number and duration of episodes of pain in the heart. After a two-month period of treatment, results of life quality assessment in this group were significantly different from those before treatment: EQ-5D-index was 0.851 ± 0.059 ($p < 0.001$), EQ-5D-VAS — 65.47 ± 5.19 ($p < 0.001$). Patients treated with quercetin also had a positive dynamics of subjective condition: EQ-5D-index was 0.839 ± 0.037 ($p < 0.01$), EQ-5D-VAS – 62.92 ± 5.82 ($p < 0.001$). In the comparison group after treatment EQ-5D-index also increased 0.809 ± 0.057 (< 0.001), EQ-5D-VAS rather significantly changed — $58,81 \pm 6.09$ ($p < 0.01$).

After the treatment in each study group total cholesterol level and LDL cholesterol decreased, HDL cholesterol level did not change significantly (Table I). No significant differences between the results of the groups were revealed.

Analysis of hemocoagulation indicators showed that 34% of patients with stable coronary artery disease at initial examination had increased fibrinogen concentration in the blood (norm – 2-4 g/L). Before treatment significant differences of that indicator in the groups were not revealed (Table II). The treatment resulted into a significant decrease in fibrinogen concentration, more pronounced in patients treated with resveratrol ($p = 0.0001$) and quercetin ($p = 0.0004$) than in the control group ($p = 0.002$). Other indicators of hemocoagulation (PTI, aPTT, INR) did not exceed the physiological norms before treatment, after the treatment they did not significantly change.

In patients with stable coronary artery disease, an increased amount of EMP CD32⁺CD40⁺ in the blood was found, which confirms the presence of ED (Table II). The number of EMP CD32⁺CD40⁺ in healthy individuals is 1.30×10^7 /L with a range of values in Q1-Q3 quartiles $(1.05 - 2.11) \times 10^7$ /L. Under the conventional therapy the number of EMP CD32⁺CD40⁺ did not change ($p = 0.548$), as well as in the group of patients treated with

Table I. Indicators of lipid blood profile in patients of the study groups.

Group / Mark	Statistical index	Cholesterol, mmol/l		LDL cholesterol, mmol/l		HDL cholesterol, mmol/l		Triglycerides, mmol/l	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Group of comparison	X	5,48 ±	4,74 ±	3,43 ±	2,74 ±	1,12 ± 0,24	1,16 ± 0,17	2,11 ±	1,91 ±
	σ	1,05	0,61	0,76	0,52	0,061	0,042	0,54	0,35
	s_x	0,262	0,153	0,189	0,129			0,135	0,086
	p	< 0,01		< 0,001		> 0,05		< 0,05	
Group of investigation 1 (resveratrol)	X	5,38 ±	4,48 ±	3,45 ±	2,46 ±	1,03 ± 0,22	1,07 ± 0,20	2,04 ±	1,88 ±
	σ	0,90	0,75	0,79	0,60	0,052	0,047	0,37	0,35
	s_x	0,221	0,176	0,183	0,141			0,087	0,083
	p	< 0,001		< 0,001		> 0,05		< 0,001	
Group of investigation 2 (quercetin)	X	5,14 ±	4,35 ±	3,16 ±	2,42 ±	1,12 ± 0,22	1,15 ± 0,18	1,89 ±	1,71 ±
	σ	0,96	0,84	0,71	0,65	0,058	0,047	0,43	0,34
	s_x	0,257	0,223	0,19	0,173			0,114	0,091
	p	< 0,001		< 0,001		> 0,05		< 0,01	

Note: X – the sample mean, σ – standard deviation, s_x – the standard error of the mean.

Table II. The indicators of systemic inflammation and endothelial destruction in patients of the study groups.

Group/ Mark	Statistical index	TNF α , pg/ml		Fibrinogen, g/l		EMP CD32+CD40+, x 10 ⁷ /l		Statistical index
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	
Group of comparison	X	8,53	8,34	3,78	3,17	1,73	1,85	Me s_{Me} Q1-Q3
	σ	±3,24	±2,17	±0,91	±0,35	±0,23 (0,97-4,00)	±0,19 (0,94-3,56)	
	p	p=0,866		p=0,002		p=0,547*		
Group of investigation 1 (resveratrol)	X	9,69	7,28	4,06	2,92	1,93	1,40	Me s_{Me} Q1-Q3
	σ	±1,86	±2,33	±0,85	±0,41	±0,20 (1,25-4,55)	±0,13 (1,09-2,59)	
	p	p=0,013		p=0,0001		p=0,038*		
Group of investigation 2 (quercetin)	X	7,80	5,98	3,53	2,71	1,8	2,11	Me s_{Me} Q1-Q3
	σ	±2,44	±1,81	±0,63	±0,77	±0,26 (0,98-4,93)	±0,13 (1,15-3,93)	
	p	p=0,060		p=0,0004		p=0,221*		

Note: X – the sample mean, σ – standard quadratic deviation, Me – median, s_{Me} – the standard error of the median, Q1 - Q3 – upper and lower quartiles; * – Wilcoxon (U).

additional quercetin ($p = 0.312$). A statistically significant decrease of EMP CD32+CD40+ proved to be under resveratrol ($p = 0.038$).

Also, every patient before treatment revealed increased TNF- α in the blood (normal value – 0.5 (0-6) pg/mL). A statistically significant decrease in TNF- α under resveratrol ($p = 0.013$) and a tendency to its decrease in patients treated with quercetin ($p = 0.06$) (Table II) was found out.

Between the number of EMP and other indices studied correlations have not been identified, which may indicate a narrow specificity of EMP as an independent marker of ED. In addition to sound close direct correlation between cholesterol, triglycerides and LDL cholesterol, moderate correlations between fibrinogen and TNF- α , cholesterol, LDL cholesterol and triglyceride levels have been found out (Table III).

Table III. The correlation coefficients between the indicators of lipid blood profile, endothelial dysfunction and inflammatory mediators in patients with stable coronary artery disease.

EMP CD32 ⁺ CD40 ⁺	-	-	-	-	-	
Triglyce-rides	-	0,412**	0,736***	0,401**		
LDL-cholesterol	0,358**	0,401**	0,944***			
Chole-sterol	0,270*	0,355**				
Fibrinogen	0,352**					
TNF α						
	TNF α	Fibrino-gen	Chole-sterol	LDL-chole-sterol	Triglyce-rides	EMP CD32 ⁺ CD40 ⁺

Note: * – ($p < 0.05$), ** – ($p < 0.01$), *** – ($p < 0.001$).

DISCUSSION

The revealed correlations between the indices of lipid spectrum of the blood and mediators of chronic SI confirmed their close pathogenetic cooperation in the conditions of atherogenesis [2, 15]. This study has shown normalization of blood lipid parameters in each group with no significant predominance. In respect that patients of each study group received statins as basic therapy, probably lipid-lowering effect of resveratrol and quercetin did not exceed that of statins.

While stable coronary artery disease in our research, no significant changes in blood coagulation potential have revealed, except for the content of fibrinogen, which increase should be considered, to a greater extent, as systemic inflammation factor. Probably, coagulation changes, characteristic for CAD, such as activation factor XII, increased synthesis of thromboxane A2 with an excess of arachidonic acid when chronic SI, reducing the formation of tissue plasminogen activator and antithrombin III ET, heparin depletion as a co-enzyme of lipoprotein lipase with hyperlipidemia, to a greater extent, are implemented into destabilization of the clinical course and the development of atherothrombosis.

As a reactant of acute phase of inflammation, fibrinogen increases the expression of NF- κ B in mononuclear phagocytes by CD11b/CD18 receptors, which contributes to the inflammatory activation, expression of monocyte chemoattractant protein – 1 (MCP-1) and the synthesis of CK (interleukin-1 β (IL-1 β , TNF- α) [16]. Fibrinogen has synergistic effect with IL-1 β in the activation of fibroblast growth factor-2 (FGF2), which leads to an increase of NF- κ B signaling in ET [17].

In this research, both studied polyphenols have had significant impact on markers of systemic inflammation (fibrinogen and TNF- α), with a predominance of the effectiveness of resveratrol. Statins have had a corrective effect on fibrinogen content in the blood only, but to a lesser extent than in combination with polyphenols studied. Probably, for the implementation of the pleiotropic anti-inflammatory effect of statins it is necessary to use higher doses, according to the current guidelines, or a longer period of exposure to the drug is needed. We chose an empirical approach to choose doses of statins not to disguise

the effects of polyphenols studied, but to explore the possible benefits of the combination of these drugs.

ED is the earliest stage of atherogenesis, at the same time it plays a leading role in the progression of vascular changes, in the formation of atheromatous plaques, their destabilization [4]. According to the scientific data, statins increase the activity of endothelial NO-synthase (eNOS), reduce the formation of CK, providing endothelioprotection. Quercetin is also due to membrane-protective properties helps to protect the ET [18]. In this study neither quercetin nor statins have had no significant effect on the level of degradation of ET — EMP. Perhaps, the reason for it is the low dose of statins, short follow-up and established in various studies low bioavailability of quercetin, which necessitates its use in coronary artery disease as a parenteral solution. However, over the same period a significant corrective effect of resveratrol on the pool of EMP in the bloodstream has been found out, which is a proof of its pronounced endothelioprotective effect.

In addition to the ability of resveratrol to activate eNOS, its inhibitory effect on the nuclear transcription factor kappa B (NF- κ B), which is a key element of the activation of the inflammatory cascade, insulin resistance and the implementation of mechanisms of aging, is being discussed [19, 20]. Resveratrol has a blocking effect on kappa B inhibitor kinase (I κ B), which prevents the translocation of NF- κ B into nucleus and activation of the respective genes encoding cytokines, proliferation signaling molecules, chemoattractants, adhesion molecules [19, 20]. The action of resveratrol by sirtuin-activating proteins, in particular sirtuin-1, providing nucleotide skeleton density and preventing inclusions of pathogenic genes, has also been proved [9, 21]. Apparently, it is the mechanism which is the basis of the detected endothelioprotective effect of resveratrol.

There are some studies to demonstrate the inhibitory effect of quercetin on NF- κ B-dependent gene expression by reducing the TNF- α production [22]. Under the conditions of this study only a tendency to decrease TNF- α under quercetin has been observed, that probably has not been sufficient to achieve its effects relatively to NF- κ B (Table II).

Based on the results of this research, it should be assumed that resveratrol and quercetin potentiate the direct and pleiotropic effects of statins.

CONCLUSION

Thus, due to a wide range of its biological activity, resveratrol, within 2 months of treatment, to a greater extent than quercetin, has a positive effect on the function of ET and severity of systemic inflammation.

Resveratrol may provide anti-ischemic effect on coronary artery disease due to the regulation of intracellular cascades, controlling cell metabolism, antioxidant effects, endothelioprotection, slowing the formation of atherosclerotic lesions that allows to recommend it for widespread use in clinical practice as a promising angioprotector.

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