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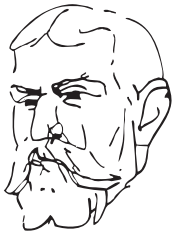

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ORIGINAL ARTICLE

INDICATORS OF ENDOTHELIAL DYSFUNCTION, MARKERS OF INFLAMMATION AND LIPID METABOLISM IN PATIENTS WITH HYPERTENSION WITH THE ADMINISTRATION OF QUERCETIN

DOI: 10.36740/WLek202207107

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ABSTRACT

The aim: To improve the effectiveness of treatment of patients with hypertension using metabolic therapy based on the evaluation of endothelial dysfunction indicators, markers of inflammation, and blood lipid spectrum.

Materials and methods: A clinical study was performed with 72 patients (34 male and 38 female) with stage 2 arterial hypertension of 2-3 degrees, admitted to the cardiology department of the municipal non-profit enterprise "Lviv Emergency Clinical Hospital". The mean age of patients was 44.8±8.5 years. Patients were divided into 2 groups: Group I was taking quercetin in addition to basic therapy (Ramipril/Amlodipine in individually adjusted dose); Group II – had basic therapy following the clinical protocol. The level of nitric oxide, IL-1, IL-6, TNF-a, CRP, seromucoid, blood lipid spectrum was determined.

Results: There is a significant decrease in the NO and CRP levels. There is a decrease in the TNF-a level by 31.27±2.13 ($p<0.01$) after the treatment of patients with hypertension. The TNF-a level decreased by 22.2±1.13 ($p<0.01$) with the use of basic therapy. IL-1 decreased significantly in the two groups, but it was more pronounced in group I, by 40.68±1.67 ($p<0.01$) and 21.4±2.1 in group II ($p<0.05$). There is a positive change in the blood lipid spectrum, but the changes were more pronounced in the group of patients receiving metabolic therapy.

Conclusions: The use of quercetin (Corvitin, Quertin) in combination therapy with the combined antihypertensive drug containing ramipril/amlodipine (Egis-Hungary) significantly reduces the levels of nitric oxide, CRP, IL-1, and blood lipid spectrum, which reduces the incidence of complications and progression of hypertension.

KEY WORDS: endothelial dysfunction, TNF-a, IL-1, IL-6, CRP, lipid spectrum, hypertension, amlodipine, ramipril, quercetin

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INTRODUCTION

Systemic endothelial dysfunction (ED) is a risk factor of cardiovascular complications in various diseases. There is a stable relationship between indicators of endothelial damage and coagulation disorders, atherogenesis, and the level of proinflammatory cytokines [1-4]. Arterial hypertension is one of the most important factors of atherosclerosis, the inalienable conditions of which are oxidative stress, endothelial dysfunction, and low-grade inflammation, which remains a leading cause of death all over the world [5].

ED is considered as the main mechanism of formation of hypertension and its complications [6]; it is involved in the pathological process in the earliest stages of hypertension [7]. The term "endothelial dysfunction" should primarily be understood as changes in the functional state of the endothelium, which is a response to external stimuli and have protective functions [8]. However, prolonged exposure to pathogenic factors leads to a gradual development of endothelial dysfunction, which is expressed in an imbalance between mediators, which normally provide the optimal course of all endothelium-dependent processes [9] between hypertension and atherothrombotic cardiovascular complications.

The endothelium is one of the systemic "target organs" in hypertension, damage to which plays an important role in the development of cardiovascular complications. The mechanism of endothelial involvement in the onset and development of various pathological conditions is many-sided and associated not only with the regulation of vascular tone but also with participation in the process of atherogenesis, thrombosis, protection of the vascular wall integrity. The endothelium performs a barrier function to maintain homeostasis by maintaining a dynamic balance among several multidirectional processes of vascular tone regulation (vasodilation/vasoconstriction), anatomical structure and remodeling of blood vessels (synthesis/inhibition of proliferation factors), local inflammation (production of anti-inflammatory factors, regulation of vascular permeability, leukocyte adhesion processes), hemostatic and thrombolytic processes (synthesis and inhibition of platelet aggregation factors and fibrinolysis) [10].

Depletion and changes in endothelial function occur with prolonged exposure to various factors (hemodynamic overload, hypoxia, intoxication, inflammation). Decreased nitric oxide concentration causes vasocon-

striction, stimulation of platelet aggregation, adhesion of platelets and leukocytes, growth and proliferation of smooth muscle cells [11]. In this case, the intensive production of peroxide radicals disturbs the balance between protective and damaging effects on the vessel wall, which realize their harmful effects due to the intensification of oxidative stress processes. The formation of superoxide anion and endothelin-1 is the consequence of this [12]. All these changes provoke the development of local and systemic complications that contribute to the accumulation of lipids in the subendothelial space, where chemical modification of low-density lipoprotein (LDL) can occur.

Modified LDL attract monocytes into the vascular wall, where they turn into macrophages, absorb modified lipoproteins. Unregulated uptake of modified LDL leads to the formation of large foam cells characteristic of fatty streaks, which subsequently lead to the progression of atherosclerosis [13].

The failure of the hemostasis system plays a certain role in a complex system of mechanisms that contribute to the development of atherosclerotic changes in blood vessels [10]. Atherosclerotic and associated inflammatory vascular lesions increase platelet activity, their readiness for aggregation and adhesion, activate plasma coagulation factors such as fibrinogen, and inhibit the anticoagulant system and fibrinolysis [14].

NO deficiency is one of the defining elements of endothelial dysfunction. NO is a signaling molecule involved in the regulation of several physiological processes, such as vasodilation, transmission of nerve impulses, and the immune response. NO affects vascular tone, proliferation and apoptosis, regulation of oxidative processes. NO has angioprotective properties [15], is responsible for anti-inflammatory effects, such as inhibition of the expression of cell adhesion molecules ICAM-1 (intercellular adhesion molecules-1), VCAM-1 (vascular cellular adhesion molecules-1), and tissue factor; inhibition of the chemokine release, such as MCP-1 (monocyte chemoattractant protein-1). NO blocks platelet aggregation and has a fibrinolytic effect [16].

The substrate for NO synthesis is a flavonoid – quercetin, which can reduce the activation and adhesion of leukocytes and platelets to the vascular endothelium, inhibits the synthesis of VCAM-1 and MCP-1 adhesion proteins, thus preventing the formation and development of atherosclerotic plaques, inhibits the synthesis of endothelin-1, which is a powerful vasoconstrictor and stimulator of proliferation and migration of smooth myocytes of the vascular wall. It has pronounced antioxidant, antiradical, membrane-stabilizing properties, antiplatelet effect, prevents an increase of potassium level in cells, has a vasoprotective effect, inhibits protein kinase, has a pronounced cardioprotective activity [17].

THE AIM

To improve the effectiveness of treatment of patients with stage 2 arterial hypertension, 2-3 degrees using metabolic therapy based on the evaluation of endothelial dysfunction indicators, inflammatory activity, and lipid metabolism.

MATERIALS AND METHODS

A clinical study was performed with 72 patients with stage 2 arterial hypertension of 2-3 degrees, admitted to the cardiology department of the municipal non-profit enterprise "Lviv Emergency Clinical Hospital". Randomization was performed using random numbers. The results of NO concentration, CRP, seromucoid, IL-1, IL-6, TNF-α levels, and lipid spectrum in blood and serum of patients with stage 2 hypertension of 2-3 degrees are presented. 72 patients (34 male and 38 female) were examined. The mean age of patients was 44.8±8.5 years. The study groups did not differ in age composition, severity of disease and other outcomes that could affect the final results of the study. The study did not include patients with severe cardiac, hepatic, and renal failure, cancer, alcoholism, or drug addiction. The study was approved by the local bioethics committee and conducted in accordance with the principles of the Declaration of Helsinki. The patients were given general clinical and instrumental examination methods, they were determined the indicators of proinflammatory cytokines (interleukin-1β (IL-1β), interleukin-6 (IL-6), necrosis factor of alpha tumors (TNF- α)), C-reactive protein (CRP), nitrogen oxide (NO) and seromucoid. Examination of patients was performed on entry to the hospital.

Hypertensive patients received basic combination antihypertensive therapy using ramipril/amlodipine in individually adjusted doses: 5/5; 5/10; 10/5; 10/10, in combination with metabolic therapy with quercetin – corvitin at a dose of 0.5 g dissolved in 50 ml of isotonic sodium chloride solution IV b.i.d. after 12 hours for 5 days; the following 30 days of outpatient treatment, patients received quertin 40 mg t.i.d. orally.

Patients were divided into 2 groups: Group I (study) including 39 patients with stage 2 hypertension of 2-3 degree taking quercetin in addition to basic therapy; Group II (comparison) including 33 hypertensive patients who received basic therapy following existing standards. The study was performed three times: 1st time – on admission; 2nd time – on the day of discharge (on 10th – 12th day of inpatient treatment), 3rd time – on 30th day after the end of treatment with quertin.

Evaluation of total cholesterol and lipid fractions was performed using the enzyme-linked immunosorbent assay (ELISA) on the FP-900 analyzer (Finland), latex turbidimetric immunoassay was used in the laboratory of MNE "LECH" to study the CRP, seromucoid levels. A set of BMS810F reagents, manufactured by MedSystems GmbH – Austria, was used for ELISA of the IL-1; IL-6, TNF-a levels.

Statistical processing of the results was performed using Microsoft Office Excel 2007 and "Statistica 10.0". The reliability of the results was assessed using nonparametric and Student's t-test. The difference was considered significant ($p<0.05$).

Table I. Dynamics of changes in TNF-α, IL-1, IL-6, CRP, NO, and seromucoid in patients with hypertension.

Indicator	Patients receiving basic and metabolic therapy, n=39		Patients receiving basic therapy, n=33	
	Before treatment	After treatment	Before treatment	After treatment
TNF-α, pg/ml	52.56±1.23	36.41±1.17 **	51.72±1.21	40.35±1.18*
IL-1, pg/ml	76.14±3.93	45.16±2.78 *	75.6±3.2	59.40±3.5
IL-6, pg/ml	19.41±1.35	14.03±1.2	19.67±1.4	17.31±1.3
CRP, mg/L	8.2±0.21	5.1±0.18 *	9.3±0.34	7.4±0.326*
Seromucoid, g/L	0.48±0.12	0.36±0.08	0.54±0.15	0.47±0.04
NO	50.04±15.1	34.51±13.75 *	48.97±29.84	33.79 ± 11.12

Note: * — p<0.05, ** p<0.01

Table II. Changes in blood lipid spectrum in patients with hypertension

Indicators, mol/L	Patients receiving basic and metabolic therapy, n=39		Patients receiving basic therapy, n=33	
	Before treatment	After treatment	Before treatment	After treatment
Total cholesterol	6.89±0.82	5.39±0.85	6.73±0.73	5.66±0.73
HDL	1.15±0.34	1.12±0.41	1.18±0.4	1.16±0.31
LDL	4.43±0.63	3.4±0.64	4.24±0.29	3.58±0.43
VLDL	0.97±0.081	0.67±0.088 *	0.95±0.079	0.85±0.089*
Triglycerides	2.89±0.38	1.92±0.41	2.89±0.42	2.04±0.39
AI	4.99±0.95	3.81±0.84	4.70±0.30	3.87±0.38

Note: * — p<0.05, ** p<0.01

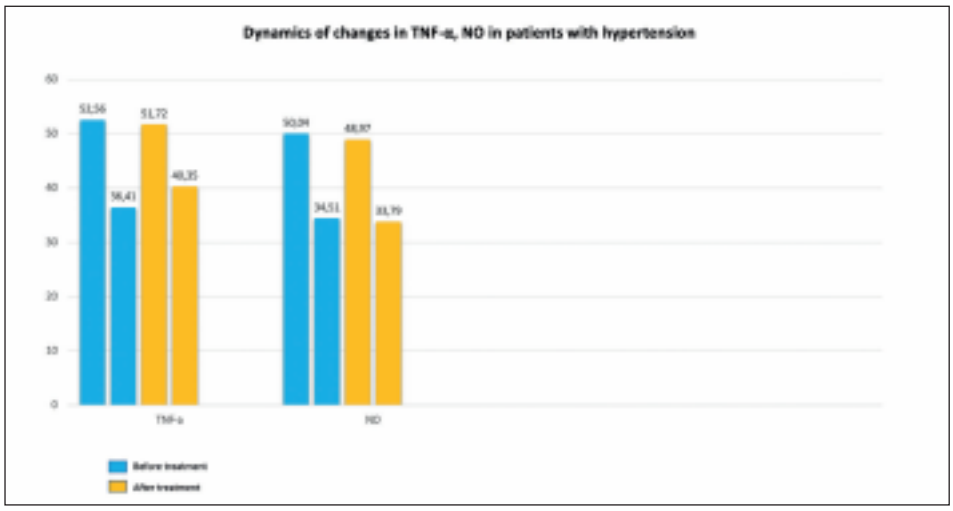

Fig. 1. Dynamics of changes in TNF-α. NO in patients with hypertension

RESULTS

According to the study, patients receiving metabolic therapy have decreased TNF-a level by 31.27±2.13 (p<0.01), while the TNF-a level decreased by 22.2±1.13 using basic therapy (p<0.01). IL-1 decreased significantly in the two groups but it is more pronounced in group I, by 40.68±1.67 (p<0.01) and 21.4±2.1 (p<0.05), respectively. There was a significant decrease in CRP and NO levels, (Tabl. I, fig. 1).

Positive changes were detected in lipid profile after treatment of patients with hypertension, but they were more pronounced in the group of patients who received additional metabolic therapy: the total cholesterol level decreased during treatment by 21.6% (5.29±0.85 after treatment), vs. 13.6% (5.81±0.89) and 15.8% (5.66±0.73) in patients receiving only basic therapy. The LDL level in both groups decreased; in group I, it decreased by 23.6% (3.41±0.56), in group II – by 15.6% (3.59±0.31).

LDL rates decreased significantly by 30.9% (0.67±0.088) compared with the results before treatment in group I, in contrast to group II, where the value decreased by only 10.5% (0.85±0.089).

The triglyceride level tended to decrease in the group of patients who were prescribed metabolic therapy by 33.5% (1.92±0.41); the decrease in triglycerides was less pronounced in the comparison group (group II) – 29.4% (2.04±0.39).

In the evaluation of HDL – significant differences between the indicators of both groups of patients were not observed; HDL increased by 2.5% (1.18±0.28) in the study group of patients taking quercetin, and the HDL level was 1.11±0.32 in the group with basic therapy.

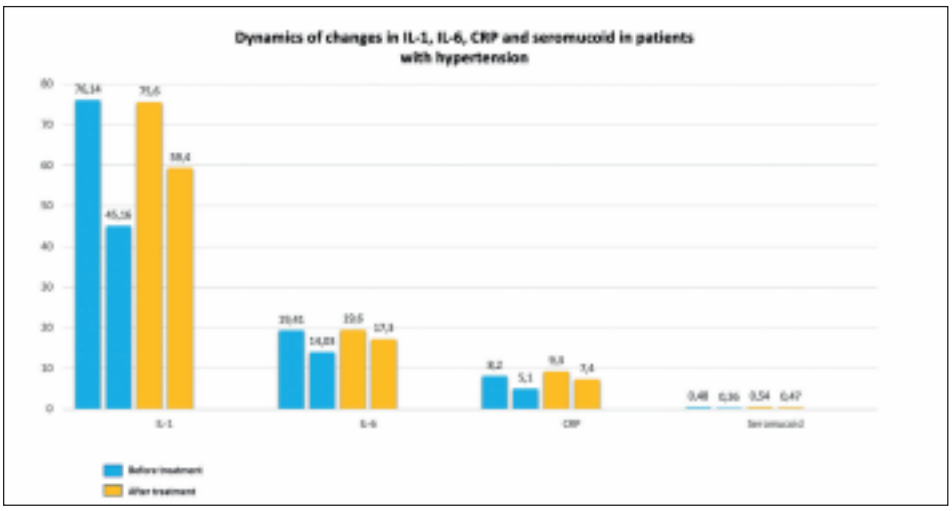

Fig. 2. Dynamics of changes in IL-1, IL-6, CRP and seromucoid in patients with hypertension

After the course of treatment, the atherogenic index (AI) decreased by 23.6% (3.81±0.84) and 17.6% (3.87±0.38) in the comparison group, but the level of atherogenic index remained elevated in both groups of patients, (Tabl. II, fig. 2).

DISCUSSION

Endothelial dysfunction is characterized by inadequate (increased or decreased) formation in the endothelium of various biologically active substances. One of the methods of assessing the severity of endothelial dysfunction is to determine blood factors that damage the endothelium, the level of which correlates with endothelial dysfunction. Such factors include hypercholesterolemia, cytokines (interleukins, tumour necrosis factor (TNF). [18].

ED is the initial stage in the pathogenesis of atherosclerosis. In vitro, a decrease in the N0 production in endothelial cells in hypercholesterolemia. Insufficient N0 synthesis contributes to free radical damage of cell membranes. Oxidized LDL enhance the expression of adhesion molecules on the surface of endothelial cells, promoting monocytic infiltration of the subendothelium. In turn, adequate N0 synthesis inhibits processes in the nucleus of atherosclerotic lesions, including platelet aggregation, monocyte adhesion and migration, vascular smooth muscle cell proliferation, and vasoconstriction [19].

It has been found experimentally that quercetin can directly inhibit major inflammatory mediators by inhibiting histamine secretion and the activity of alloantigen-specific cytotoxic T lymphocytes, IL-8 interleukin, and tumour necrosis factor (TNF-α). High antihistaminic quercetin activity has been clinically confirmed. Quercetin may interact with the calcium-mobilizing polyphosphoinositide system and other elements of this signalling cascade. It modulates many intracellular responses, including the formation and secretion of inflammatory mediators, blood clotting processes, smooth muscle contraction, some immune responses etc.. In preclinical in vitro studies, quercetin showed a significant decrease in the level of inflammatory markers (NO-synthase, COX-2 and C-reactive protein in human hepatocyte cell culture) [20].

Studies have shown that quercetin can act as an arterial vasodilator, particularly in the coronary arteries, by increasing cAMP levels in endothelial cells and inhibiting platelet aggregation [20].

Interest in quercetin as a means of prevention and treatment of COVID-19 has already found a response from many experts taking into account the urgency of the problem. In particular, Dr P. Marik recommends an updated (April 15, 2020) treatment protocol for COVID-19 patients called "Critical Care COVID-19 Management Protocol" (evmc.edu/covidcare) [21].

The use of quercetin in the treatment of patients with hypertension helps to restore the functional state of the endothelium, as it has antihypoxic, membrane-stabilizing, antioxidant properties. Its positive effects are shown in patients with coronary artery disease, hypertension, metabolic syndrome, and associated cardiac conditions, as well as in almost all components of the cardiovascular continuum [2, 4, 6, 7].

CONCLUSIONS

1. The use of quercetin (corvitin, quertin) in combination therapy with the combined antihypertensive drug containing ramipril/amlodipine significantly reduces the level of nitric oxide, CRP, IL-1, and blood lipid spectrum, which reduces the incidence of complications and progression of hypertension.
2. Quercetin in therapeutic doses has proven efficacy, high safety, and good tolerability, with the absence of severe side effects, which enhances the effectiveness of combination antihypertensive therapy.
3. The use of quercetin (corvitin, quertin) in combination with conventional antihypertensive therapy improves the performance of the endothelium and its NO-synthesizing ability.

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The Author declare no conflict of interest.

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A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

Pallas Kliniken

Kliniki Pallas specjalizują się w okulistyce i medycynie estetycznej. Zatrudniamy ponad 350 pracowników w 18 lokalizacjach i jesteśmy jednym z wiodących świadczeniodawców w Szwajcarii. Poprzez innowacje stale rozwijamy naszą ofertę usług w tych dziedzinach. Czy to poprzez nowe metody leczenia, sprzęt, dodatkowe lokalizacje i współpracę, a może poprzez współpracę z Państwem w najbliższej przyszłości?

W celu uzupełnienia istniejącego zespołu w naszej grupie w lokalizacjach **Olten, Aarau i Solothurn** poszukujemy osoby z inicjatywą i niezależną osobowością na stanowisko

specjalista oftalmologii (k/m/i) 60–100%

Główne obowiązki

Specjalista oftalmologii w naszych placówkach w Olten, Aarau lub Solothurn zapewnia profesjonalną obsługę medycznych konsultacji zachowawczych. Osoba ta będzie kompetentnie wykorzystywać swoje umiejętności we współpracy z obecnymi lekarzami specjalistami. Do jej obowiązków będzie należało zapewnienie naszym pacjentom optymalnej opieki. Wraz ze zgranym zespołem będzie świadczyć usługi medyczne na najwyższym poziomie. Będzie korzystać z szerokiej sieci wybitnych lekarzy, ciągłych szkoleń wewnętrznych i zewnętrznych oraz nowoczesnego środowiska pracy.

Profil kandydata

- Specjalizacja w dziedzinie oftalmologii
- Kilkuletnie doświadczenie w dziedzinie oftalmologii
- Przedsiębiorcze myślenie i działanie zorientowane na sukces i cel, z wysokim zrozumieniem jakości i obsługi
- Wysoka inteligencja emocjonalna i odporność w kontaktach z pacjentami, pracownikami oraz innymi partnerami wewnętrznymi i zewnętrznymi
- Umiejętność szybkiego rozpoznawania problemów i samodzielnego opracowywania rozwiązań
- Wybitne kompetencje doradcze w języku niemieckim, wyrażane w mowie i piśmie w sposób zrozumiały i adekwatny do adresata

Nasza oferta

W ramach udzielania konsultacji udostępniamy nowoczesną infrastrukturę, w której można profesjonalnie leczyć pacjentów, zarówno ambulatoryjnie, jak i stacjonarnie. Zapewniamy optymalne i jak najlepsze wsparcie podczas pracy. Oprócz uregulowanych godzin pracy (brak dyżurów nocnych i niedzielnych), które pozwalają na spędzanie czasu z rodziną i czas wolny, oferujemy także możliwości szkoleń wewnętrznych i zewnętrznych. Chętnie udzielimy dodatkowego wsparcia podczas stawiania pierwszych kroków w Szwajcarii.

Wykorzystując swoje wieloletnie doświadczenie, innowacyjność, a przede wszystkim umiejętność aktywnego słuchania, mogą Państwo naszym pacjentom pozwolić odczuć wyraźną różnicę.

Szukają Państwo wszechstronnej i ciekawej pracy w rodzinnej grupie przedsiębiorstw? Prosimy o przesłanie swojej aplikacji.

Dodatkowych informacji udziela pan Melvin Fankhauser, HR Recruiter/doradca HR ds. lekarzy, tel. +41 58 335 31 84 lub e-mail: melvin.fankhauser@pallas-kliniken.ch

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