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Efficacy of quercetin and the role of endothelial protection in the treatment of patients with arterial hypertension

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Introduction: The article presents the findings of a clinical trial investigating the impact of quercetin, as an adjunct to antihypertensive therapy, on endothelial function and daily blood pressure profiles.
The aim of the study. To conduct a comparative analysis of the impact of quercetin on 24-hour blood pressure monitoring parameters and cytokine profiles in patients with hypertension.
Materials and methods: A total of 120 patients with stage II hypertension (66 female and 54 male) were enrolled in the study. Patients were divided into 2 groups: Group I (study) – 58 patients who took quercetin (Corvitin®) in addition to basic therapy; II group (comparison) – 62 patients who underwent only basic antihypertensive therapy (Ramipril/Amlodipine).
The results and disscusions: During the administration of quercetin along with the standard basic therapy with the combination of Ramipril/Amlodipine in patients with stage II hypertension of 2–3 degrees of severity, more pronounced significant in the major indices of 24-hour BPM were observed, an increase in the ratio of subjects with a „dipper" profile due to a decrease in the number of patients with an insufficient reduction in nocturnal BP, an excessive drop in nocturnal BP or its persistent increase. Quercetin reduced markers of endothelial dysfunction, including sVCAM, sICAM-1, ET-1, IL-1α, IL-6, and TNF-α, more effectively than standard therapy alone. Standard antihypertensive therapy had a minimal effect on IL-1α and ET-1 levels.
Conclusion: The use of quercetin reliably reduces the levels of cytokines, which ensures a reduction in the manifestations of endothelial protection and contributes to better control of all blood pressure indices and normalization of the daily profile of blood pressure.

Key words: endothelin-1, arterial hypertension, ramipril/amlodipine, quercetin.

Účinnost kvercetinu a role protekce endotelu při léčbě pacientů s arteriální hypertenzí

Klinická studie hodnotila modifikaci endoteliální funkce a diurnálního rytmu krevního tlaku u pacientů s hypertenzí při použití kvercetinu jako cytoprotektivní složky kombinované antihypertenzní terapie.

Klíčová slova: endotelin-1, arteriální hypertenze, ramipril/amlodipin, kvercetin.

Introduction

The endothelium is an independent organ of internal secretion that regulates the tone of blood vessels, protects them from the negative effects of circulating cells and substances, regulates the processes of tissue homeostasis, cell migration and proliferation, controls immune, inflammatory, reparative processes, determines the filtration capacity of the kidneys, the diffusion of water and electrolytes, metabolic products, etc. (1). Violation of the functions of the endothelium - endothelial

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dysfunction (ED) - is one of the early and important components of the pathogenesis of many diseases, namely hypertension, diabetes, cardiovascular diseases, systemic autoimmune diseases, etc., as well as their complications (2). The endothelium is the target organ in hypertension, it is the first to come into contact with biologically active substances and the first to be damaged. At the same time, the endothelium implements many links in the pathogenesis of hypertension, directly affecting the increase in blood pressure (BP). It has been established that ED plays a significant role in the formation of kidney damage and deterioration of their function. It is the initial stage and a mandatory component of damage to the vascular wall, which leads to a decrease in blood flow in the main vascular pools, in particular in the glomeruli of the nephrons. An increase in the resistance of afferent and efferent arterioles and a decrease in ultrafiltration leads to a decrease in glomerulal filtration rate (GFR). As a result of damage and impaired function of the kidney endothelium, microthrombus formation and increased proliferative processes with impaired renal microrheology are observed (3, 4).

The primary goal of treating patients with hypertension, according to international and national recommendations, is to achieve the maximum and long-term reduction in the risk of cardiovascular complications by improving the control of all blood pressure indicators, early detection and correction of subclinical damage to target organs (5).

Since endothelial dysfunction is a key pathogenetic mechanism in the development of arterial hypertension, its correction is an important direction of therapy. However, in addition to the direct effect of quercetin on the endothelium, its possible pharmacokinetic interactions with classic antihypertensive drugs should be taken into account. In particular, in vitro studies show that more than 90% of circulating amlodipine binds to plasma proteins, and this interaction may affect its bioavailability and efficacy. There is evidence that flavonoids, including quercetin, may compete with certain drugs for plasma protein binding sites, potentially altering their free (active) concentration in the blood. This mechanism may be one of the factors enhancing the therapeutic effect of combination therapy (6, 7).

The effectiveness of drug therapy is assessed primarily by the effect on the main indicators of Daily Blood Pressure Monitoring (DBPM), including due to endotheli cytoprotection, the required level of which can be achieved by prescribing an additional cytoprotective drug (8). Among the markers of endothelial dysfunction, interleukin-1 (IL-1α), interleukin-6 (IL-6), tumor necrosis factor-a (TNF-a), endothelin-1, s-ICAM-1, sVCAM, C -reactive protein (CRP). They are considered as predictors of cardiovascular risk, due to their properties of increasing the procoagulation activity of blood plasma, influencing lipid metabolism, causing disruption of endothelium-dependent dilation of arterioles, deepening ED, and damaging endotheliocytes (7).

NO deficiency is one of the determinants of endothelial dysfunction. NO is a signaling molecule involved in the regulation of physiological processes: dilation of blood vessels, transmission of nerve impulses, and immune response. NO affects vascular tone, proliferation and apoptosis, regulation of oxidative stress processes. NO has angioprotective properties, is responsible for anti-inflammatory effects, such as inhibiting the expression of cell adhesion molecules ICAM-1 (intercellular adhesion molecules-1 – type 1 intercellular adhesion molecules), VCAM-1 (vascular cellular adhesion molecules-1 – adhesion molecules vascular endothelium of the 1st type) and tissue factors; inhibition of the release of chemokines, in particular MCP-1 (monocyte chemoattractant protein-1 – type 1 monocyte chemotactic factor). NO blocks platelet aggregation and has a fibrinolytic effect (6, 8, 9).

The substrate for the synthesis of NO is the flavonoid quercetin, which has the ability to reduce the activation and adhesion of leukocytes and platelets to the vascular endothelium, inhibit the synthesis of adhesion proteins VCAM-1 and MCP-1, thus preventing the formation and development of atherosclerotic plaques. Quercetin suppresses the synthesis of endothelin-1, which is a powerful vasoconstrictor, stimulator of proliferation and migration of smooth myocytes of the vascular wall. It has pronounced antioxidant, anti-aggregant, anti-radical, membrane-stabilizing properties, prevents an increase in the level of potassium in cells, exhibits an angioprotective effect, inhibits protein kinase, exhibits pronounced cytoprotective (endothelial protective) activity. The use of quercetin, as an endothelium-protective drug, allows to directly influence the pathophysiological processes and characteristics of endothelial dysfunction, as evidenced by a decrease in its individual markers. In turn, this leads to the harmonization of vasomotor reactions, improvement of control of all main blood pressure indicators, correction of the daily profile of blood pressure, and improvement of the prognosis of patients (11, 12).

The aim of the study

To conduct a comparative assessment of the dynamics of indicators of daily blood pressure monitoring and changes in the levels of cytokines - markers of ED in patients with hypertension depending on the use of quercetin in treatment.

Material and methods

The medical histories of 120 patients with hypertensive disease II stage 2-3, who were undergoing inpatient treatment in the cardiology department of the regional clinical hospital in Chernivtsi, were studied and investigated. Patients were randomized according to their order of hospitalization upon admission to the hospital. Randomization of patients was carried out in the order of hospitalization of patients to a hospital.

Patients were divided into two groups: Group I (main) – 58 patients who, in addition to basic therapy, received quercetin (Corvitin®), average age (57.87 ± 13.6) years; II group (comparison) – 62 patients who received only basic antihypertensive therapy, average age (59.09 ± 12.47) years.

Patients with hypertension received basic antihypertensive therapy with a combination of ramipril and amlodipine in individually selected doses ranging from 5/5 mg to 10/10 mg. In addition to this treatment, quercetin (Corvitin) was prescribed at a dose of 0.5 g, administered intravenously twice daily (every 12 hours) for five days.

The study was conducted twice: upon admission of the patient and one day before discharge from the hospital (14th day of hospital treatment).

Daily monitoring of BP (DBPM) was carried out with the help of a BAP 41-2 device ("IKS-Techno", Ukraine). Day, night, average daily (24 hours) systolic (SBP) and diastolic (DBP) blood pressure, heart rate were

determined; indicators of „pressure load" – the time index (IR) of blood pressure separately for SBP and DBP during the day and night hours. Diurnal index (DI – the degree of nocturnal decrease in blood pressure) was calculated according to the formula: Avg. AT day + Wed. BP night / Avg. BP day × 100 %. By immunoenzymatic analysis, the concentrations of soluble forms of vascular wall endothelium adhesive molecules s-ICAM-1, sVCAM (set of reagents Human s-ICAM-1 ELISA BMS201 and Human sVCAM-1 ELISA BMS232 produced by MedSystems GmbH, Austria), ET-1 (set reagents BI-20082H, "Biomedica Medizinprodukte GmbH" Austria), IL-1α, IL-6, TNF-α (set of reagents BMS810F, manufactured by MedSystems GmbH, Austria).

Statistical data processing was carried out using Microsoft Office Excel 2007 and Statistica 10. The study was conducted at the clinical base of the Bukovinian State Medical University (Menutes of the meeting of the Bioethics Commission № 2 of October 21, 2021). All stages of the study were conducted in accordance with the Helsinki Declaration on Ethical Principles of Medical Research, the Council of Europe Convention on Human Rights and Bioethical Aspects, and the legislation of Ukraine. The reliability of the results was assessed using the Student's t-test. The difference in indicators was considered reliable at $p < 0.05$. The average value, standard errors (M±m), as well as the reliability of differences were evaluated. Pearson's correlation analysis was used to assess intergroup differences between indicators. The multiplier coefficient was calculated, the closer the R value is to 1, the closer the relationship between the performance indicator and the factors is. The effectiveness and safety of additional cytoprotective therapy was evaluated as the percentage of changes (Δ, %) in the average levels of indicators between their starting values on the first day of hospitalization and the levels determined at the end of treatment (on the 14th day of patients treatment).

The results and disscusions

Table 1 shows the dynamics of DBPM indicators in patients with stage II hypertension under the influence of complex antihypertensive therapy (group II) and with additional use of quercetin (group I): 1st and 14th day.

At the beginning of treatment, patients of both groups had insufficient control of parameters that reflect the pressor pressure load, in particular, increased levels of average daily, day and night values of SBP, DBP, IR and insufficient nocturnal reduction of SBP.

At the beginning of the study, the average daily SBP was 155.3 ± 0.52 mmHg, DBP – 79.02 ± 0.58 mm Hg. When using combined antihypertensive therapy and quercetin, daily SBP decreased to target values in 30 – 83.3 % of patients, average daily SBP decreased by 38.02 ± 0.98 mmHg to 117.58 ± 0.68 mmHg – 24.28 %, $p < 0.001$; average daily SBP – by 35.24 ± 1.49 mmHg to 123.45 ± 0.61 mmHg – 22.16%, $p < 0.05$; average night SBP – by 39.56 ± 1.18 mmHg to 113.83 ± 0.76 mmHg – 25.82%, $p < 0.05$; daily BP – by 38.02 ± 1.05 mmHg to 69.02 ± 0.73 mmHg – 28.86 %, $p < 0.0001$;

Tab. 1. *Dynamics of indicators of daily blood pressure monitoring in the 1st and 2nd groups*

Indexes	Group I (n = 58) M ± m	Absolute variable, %	Group II (n = 62) M ± m	Absolute variable, Δ %	p
Average daily systolic blood pressure 1st day	158.61 ± 0.78	35.24 ± 1.49 (22,16 %)***	163.90 ± 1.12	30.8 ± 1.71 (18.71 %)*	0.027*#
14th day	123.45 ± 0.61		133.11 ± 1.29		
Midday diastolic blood pressure 1st day	93.32 ± 0.50	22.13 ± 1.44 (23.71 %)***	100.42 ± 0.53	9.01 ± 1.16 (8.99 %)*	0.0001*** #
14th day	71.19 ± 119		91.41 ± 1.07		
Midnight systolic blood pressure 1st day	152.17 ± 0.71	39.56 ± 1.18 (25.82 %)***	153.3 ± 1.04	34.55 ± 1.52. (23.72 %)**	0.01*#
14th day	112.83 ± 0.76		116.9 ± 1.28		
Midnight diastolic blood pressure 1st day	94.23 ± 0.80	29.39 ± 1.19 (31.07 %)***	95.4 ± 0.89	24.27 ± 1.35 (25.93 %)*	0.005**#
14th day	64.95 ± 0.74		70.66 ± 1.33		
Meart rate 1st day	90.25 ± 1.66	17.14 ± 1.59 (18.99 %)***	92.72 ± 2.06	17.50 ± 1.94 (19.32 %)***	0.886
14th day	73.11 ± 0.85		74.8 ± 1.13		
Average daily systolic blood pressure 1st day	155.3 ± 0.52	38.02 ± 0.98 (24.28 %)***	157.83 ± 0.75	26.22 ± 1.52 (17.07 %)*	0.0001*** #
14th day	117.58 ± 0.68		131.6 ± 1.33		
Average daily diastolic blood pressure 1st day	79.02 ± 0.58	38.56 ± 1.05 (32.79 %)***	98.61 ± 0.66	16.42 ± 1.05 (16.6 %)*	0.0001*** #
14th day	69.02 ± 0.73		82.17 ± 0.89		
Pulse daytime BP 1st day	58.31 ± 0.53	8.61 ± 0.72 (14.47 %)***	60.31 ± 0.75	6.50 ± 1.86 (10.33 %)***	0.293
14th day	49.87 ± 0.59		54.07 ± 1.80		
Pulse night BP 1st day	57.20 ± 0.72	7.57 ± 1.10 (13.33%)***	56.84 ± 0.76	4.04 ± 1.59 (6.61 %)*	0.07
14th day	49.57 ± 0.89		53.04 ± 1.59		
Pulse daily blood pressure 1st day	57.70 ± 0.34	8.00 ± 0.74 (13.07%)***	58.21 ± 0.54	4.83 ± 1.70 (7.91 %)*	0.08
14th day	49.72 ± 0.64		53.6 ± 1.65		
Time index of systolic blood pressure 1st day	67.75 ± 1.13	50.76 ± 1.30 (74.84%)***	68.7 ± 1.66	37.61 ± 2.18 (54.74 %)*	0.00001** #
14th day	17.04 ± 0.43		31.09 ± 1.35		
Time index of diastolic blood pressure 1st day	64.44 ± 0.72	48.71 ± 0.96 (75.23%)***	65.3 ± 1.41	35.9 ± 1.85 (54.9 %)*	0.00001** #
14th day	15.96 ± 0.46		29.4 ± 1.59		
Pressure load index 1st day	63.60 ± 1.05	46.77 ± 1.02 (73.23%)***	63.2 ± 1.10	41.07 ± 1.98 (65.9 %)***	0.01*#
14th day	17.02 ± 0.51		21.5 ± 1.61		
Daily index 1st day	8.35 ± 1.16	-5.85 ± 0.80	11.6 ± 1.19	0.20 ± 0.63	
14th day	13.66 ± 0.40		13.6 ± 0.44		

** – p < 0.05, ** – p < 0.01, *** – p < 0.001; # – significant difference p < 0.05, between indicators of I and II groups*

Tab. 2. *Comparative characteristics of the dynamics of indicators of daily blood pressure reduction*

Type of daily profile of AT	I group (n = 58)			II group (n = 62)		
	1st day	14th day	Δ %	1st day	14th day	Δ %
«dipper»	25 (43.1 %)	55 (94.8 %)	51.7 %	22 (35.4 %)	44 (70.9 %)	35.5 %
«non-dipper»	13 (22.4 %)	3 (5.17 %)	17.23 %	20 (32.2 %)	10 (16.1 %)	16.1 %
«night-peaker»	6 (10.3 %)	-	10.3 %	12 (19.3 %)	3 (4.8 %)	14.5 %
«over-dipper»	14 (24.1 %)	-	24.1 %	8 (12.9 %)	5 (8.06 %)	4.84 %

Tab. 3. *Dynamics of indicators of systemic inflammation activity and endothelial dysfunction in two groups of patients with arterial hypertension*

Indexes	I group				II group			
	1st day	14th day	Δ %	p	1th day	14th day	Δ %	p
Interleukin-1α (pg/ml)	5.34 ± 0.25	4.62 ± 0.20	13.4 %	0.0005	4.4 ± 0.24	4.03 ± 0.20	8.4 %	0.057
Interleukin- 6 (pg/ml)	7.29 ± 0.40	5.18 ± 0.29	28.9 %	0.0000	5.38 ± 0.34	4.67 ± 0.30	13.2 %	0.016
Tumor necrosis factor-α (pg/ml)	7.71 ± 0.27	6.16 ± 0.27	20.1 %	0.0000	6.28 ± 0.31	5.93 ± 0.29	5.5 %	0.043
SRP	6.54 ± 0.28	5.33 ± 0.29	18.5 %	0.003	6.31 ± 0.27	5.31 ± 0.28	15.8 %	0.001
Endothelin-1	2.54 ± 0.20	2.09 ± 0.14	17.7 %	0.000	2.92 ± 0.19	2.67 ± 0.16	8.5 %	0.31
sVCAM (ng/ml)	1117.50 ± 47.9	916.95 ± 36.1	17.9 %	0.0000	977.83 ± 44.6	851.51 ± 38.1	12.9 %	0.0002
s-ICAM-1 (ng/ml)	354.09 ± 18.1	283.76 ± 12.1	19.8 %	0.0000	335.6 ± 19.3	281.59 ± 14.6	16.0 %	0.007

s-VCAM – soluble vascular endothelium adhesion molecule; s-ICAM-1 – type I soluble intercellular adhesion molecule

average daily BP – by 28.08 ± 1.44 mmHg to 74.19 ± 1.19 mmHg – 39.91 %, p < 0.001; average night DBP – by 29.39 ± 1.19 mmHg to 64.95 ± 0.74 mmHg – 31.07 %, p < 0.01.

In the II group, a significantly smaller share – 22 (70.9 %) people managed to achieve the target daily SBP. There was also a less pronounced, although significant decrease in average daily SBP by 26.22 ± 1. mmHg to 131.6 ± 1.33 mmHg – 17.07 %, p < 0.05, average daily SBP – by 30.8 ± 1.71 mmHg to 133.11 ± 1.29 mmHg – 18.71 %, p < 0.05, average night SBP – by 34.55 ± 1.52 mmHg to 116.9 ± 1.28 mmHg – 23.72 %, p < 0.05; daily BP – by 16.42 ± 1.05 mmHg to 82.17 ± 0.89 mmHg – 16.6 %, p < 0.05.

IR dynamics during the day were analyzed in two groups. IR characterizes the „pressure load" during the day and night hours. Before treatment, high average daily IR values were observed in two groups, which indicated stable elevated blood pressure levels during the day and, accordingly, high risk cardiovascular complications in the majority of examined patients. In the dynamics of observation in the 1st group, a significant (p < 0.05) decrease in „pressure load" indicators was registered: IR SBP – by 50.76 ± 1.30 mmHg (74.84 %) to 17.04 ± 0.43 mmHg, p < 0.0001; IR DAT – by 48.71 ± 0.96 mmHg (75.23 %) to 15.96 ± 0.46 mmHg, p < 0.0001. In the II group, a less pronounced decrease in IR SBP was noted – by 37.61 ± 1.13 mmHg (54.74 %) to 31.09 ± 1.35 mmHg., p < 0.05 and IR DAT – by 35.9 ± 1.85 mmHg (54.9 %) to 29.4 ± 1.85 mmHg, p < 0.01.

At the beginning of the study in the I group more than 73–61 % patients observed a disproportionate daily rhythm: in 33–28 % of patients there was an insufficient decrease in night BP "non dipper", in 18 patients – 15 % a persistent increase in night BP "night peaker", in 22 patients – 19 % „over dipper" (Tab. 2). After treatment, in the Corvitin group, a significant improvement in the daily blood pressure profile was noted by 30–52 %, in the II group, only 22 patients managed to achieve normalization of the daily blood pressure profile – 36 % (Tab. 2).

Activation of systemic inflammation of low intensity, as a component of ED, is recognized as one of the factors in the development and progression of atherogenesis, hypertension, heart failure and aterial fibrillation. We conducted a study of the dynamics of some of its markers, in particular, CRB, IL-1α, IL-6, TNF-α, vascular endothelial adhesion molecules (s-VCAM), type I intercellular adhesion molecules (s-ICAM-1), depending on the application in quercetin treatment.

It was established that at the beginning of the study, there was a statistically significant increase in the concentration of markers of inflammation and ED in patients with hypertension, which is probably the basis for insufficient control of blood pressure, in particular, soluble adhesion molecules s-ICAM-1, sVCAM. Against the background of the treatment, there was a significant decrease in the concentration of soluble forms of adhesive molecules of the vascular wall endothelium (s-ICAM-1, sVCAM) in two groups of patients, but with a significant difference between them. In the I group of patients who additionally received quercetin, the level of ICAM-1 decreased by 19.8 %, p < 0.001 (from 354.09 ± 18.17 to 383.76 ± 12.13 ng/ml) (Tab. 3).

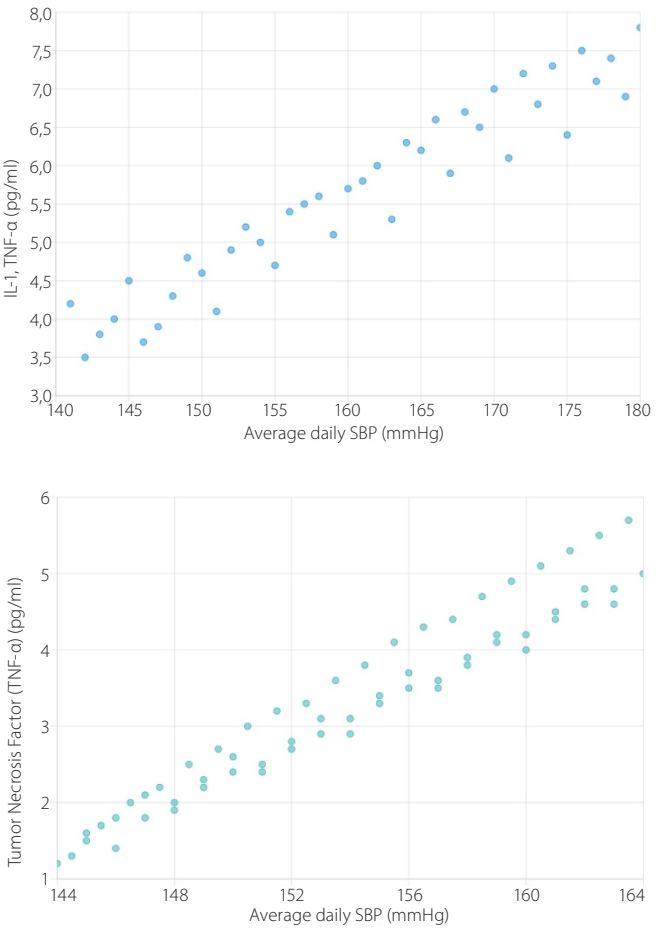
In the group that did not receive quercetin (group II), there was a decrease in the level of ICAM-1 by 16.0 % (from 335.6 ± 19.36 ng/ml to 281.59 ± 14.61, p < 0.05). The level of sVCAM in group I significantly decreased by 17.9 % (from 1117.50 ± 47.92 to 916.95 ± 36.16, p < 0.001), in group II – by 12.9 % (from 977.83 ± 44.67 to 851.51 ± 38.17, p < 0.001). The level IL-1 decreased in both groups of patients: in group I – by 13.4 % (5.34 ± 0.25 to 4.62 ± 0.20, p < 0.005), in group II – by 8.4 % (from 4.4±0.24 to 4.03 ± 0.20, p < 0.05). Levels of TNF-α and ET-1 significantly decreased in the quercetin group, respectively, by 20.1 % (from 7.71 ± 0.27 to 6.16±0.27, p < 0.005) and 17.7 % (from 2.54 ± 0.20 up to 2.09 ± 0.14, p < 0.005) (Tab. 3). At the same time, as in the II group, the dynamics of ET-1 indicators was less intense and unreliable: TNF-α decreased – by 5.5 %, (from 6.28 ± 0.31 to 5.93 ± 0.29), ET-1 – by 8.5 %, (from 2.92 ± 0.19 to 2.67 ± 0.16) (Tab. 3).

The correlation between daily average SBP and ED indicators was analyzed (Fig. 1). A reliable, direct, medium-strength relationship was established between the average daily SBP level and the IL-1α level indicator (r = 0.313, p < 0.012); IL-6 (r = 0.317, p = < 0.015); TNF-α (r = 0.307, p = < 0.019) and direct, strong relationship between average daily SBP and total cholesterol level (r = -503.2, p < 0.0001); a reliable, direct,

medium-strength (r = 303.6, p = < 0.013) relationship between mean night SBP and the level of endothelin-1 was revealed, and a direct, strong correlation between mean night DBT and concentration VCAM (r = 403.5 p < 0.0001), ICAM-1 (r = 324.1, p < 0.013).

The data of our study are consistent with the data of the clinical study of T.A. Kozhanov (2010), where the results of the influence of quercetin on the dynamics of the decrease in cytokine levels are presented. It was established that the use of quercetin in the complex treatment of patients with arterial hypertension contributes to the normalization of a number of pro-inflammatory cytokines: TGF-1, IL-1α, IL-4, TNF-α, prevents remodeling of the endothelium, reducing the manifestations of ED. According to the data of a clinical study by N. S. Mykhaylovska and T. V. Oliynyk (2016), it was established that the appointment of quercetin against the background of basic therapy contributes to a reliable decrease in endothelin-1 and a tendency to a decrease in the level of tissue plasminogen activator inhibitor-1, which indicates an improvement in functional state of the endothelium, there is a decrease in the activation of the systemic inflammatory process due to a probable decrease in the activity of TNF-α, as well as a tendency to decrease the concentration of PSA. In the work of Korkushko O.V. (2021), the author noted that quercetin has a complex beneficial effect on endogenous cardiovascular risk factors: it contributes to the normalization of blood pressure, the function of the endothelium of microvessels, indicators of carbohydrate and lipid metabolism. The vasoprotective effects of quercetin are realized due to its ability to reduce the activity of the inflammatory process in the endothelium of vessels, to increase the activity of endothelial NO-synthase (eNOS), which, in turn, increases the level of nitric oxide in endothelial cells and leads to the improvement of endothelial function, statistically significantly reduces the level of systolic blood pressure and shows a tendency to lower diastolic blood pressure.

Fig. 1. *Correlation between average daily SBP and IL-1α, TNF-α*



Conclusions

1. When using quercetin along with the standard basic therapy with the combination of ramipril/amlodipine in patients with arterial hypertension II stage 2–3 of severity, a more pronounced reliable positive dynamics of the main indicators of daily blood pressure monitoring was observed, an increase in the proportion of patients with the "dipper" profile according to due to the decrease in quantity patients with insufficient reduction of night blood pressure "non diper", excessive reduction of night blood pressure "night peaker" or persistent increase of it "over dipper".

2. Augmentation of basic therapy with quercetin enhances the correction of endothelial dysfunction markers. Specifically, quercetin significantly reduces circulating levels of soluble vascular cell adhesion molecule-1 (sVCAM-1), soluble intercellular adhesion molecule-1 (sICAM-1), endothelin-1, interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). While improvements in IL-1β and endothelin-1 levels were observed, these changes were less pronounced and lacked statistical significance.

3. Given that arterial hypertension is a chronic disease, an important question remains regarding the duration of the therapeutic effect of quercetin and the impact of its long-term use on blood pressure indicators. In our study, quercetin was administered for a short period of 5 days. This period allowed us to record significant positive changes in the main indicators of daily blood pressure monitoring and markers of endothelial dysfunction.

However, further clinical studies are needed to confirm the stability of the results obtained and to determine the optimal dosage regimen for long-term use. Long-term use of quercetin as an adjunctive therapy for hypertension requires careful study of its effect on controlled parameters, as well as assessment of potential side effects that may occur. This is a key area for future research in this field.

Correlation analysis shows the close relationship between the decrease in the main indicators of daily blood pressure monitoring and the decrease in the concentration of cytokines, which characterize the state of endothelial dysfunction and systemic inflammation.

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