DOI 10.26724/2079-8334-2021-1-75-18-22
UDC 616.12-008.331.1-085:616-008.9

O.M. Bilovol, I.I. Kniazkova, N.V. Kuzminova[1], O.M. Kirienko, L.P. Abramova, A.O. Gavrylyuk[1]
Kharkiv National Medical University, Kharkiv
[1]National Pirogov Memorial Medical University, Vinnytsya

THERAPEUTIC EFFICACY OF QUERCETIN IN PATIENTS WITH ARTERIAL HYPERTENSION AND METABOLIC SYNDROME

e-mail: sskripka72@gmail.com

The purpose of our research was to increase the effectiveness of the therapy of the patients with hypertension and metabolic syndrome. 56 patients with hypertension, and metabolic syndrome were examined. After registration of the baseline data in addition to baseline therapy Quercetinum 40 mg 3 times a day for 2 months was administered to 30 patients (group 1). Basic therapy was administered to 26 patients (group 2). After treatment in group 1, the levels of office systolic and diastolic blood pressure were 7.6 % and 6.9 % ($p<0.05$), and the average daily systolic and diastolic blood pressure (according to daily blood pressure monitoring) were 8.6 % and 8.1 % ($p<0.05$) lower than in group 2. In group 1 positive changes in lipid and carbohydrate metabolism were registered. It was found that the decline of tumor necrosis factor-α levels in group 1 were significantly higher (38.6 %, $p<0.05$) than in group 2 (20.6 %, $p<0.05$). Group 1 patients showed significantly decreased of malonic dialdehyde (Δ-37.5 % vs Δ-15.7 % in group 2, $p<0,05$) and increased of superoxide dismutase activity (Δ30.4 % vs 9.0 %, respectively, $p<0.05$). Thus, addition of Quercetinum to patients with hypertension and metabolic syndrome increases the efficacy of antihypertensive therapy, positively affects on glucometabolic parameters, plasma levels of tumor necrosis factor-α and antioxidant status.

Key words: hypertension, metabolic syndrome, lipid peroxidation, tumor necrosis factor-α, quercetin.

О.М. Біловол, І.І. Князькова, Н.В. Кузьмінова, О.М. Кирієнко, Л.П. Абрамова, А.О. Гаврилюк

ТЕРАПЕВТИЧНА ЕФЕКТИВНІСТЬ КВЕРЦЕТИНУ У ПАЦІЄНТІВ З АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ ТА МЕТАБОЛІЧНИМ СИНДРОМОМ

Метою нашого дослідження було підвищення ефективності терапії пацієнтів з артеріальною гіпертензією та метаболічним синдромом. Обстежено 56 хворих на артеріальну гіпертензію та метаболічний синдром. Після реєстрації вихідних даних до базисної терапії 30 пацієнтам (1 група) додавали кверцетин 40 мг 3 рази на день протягом 2 місяців. Базисну терапію проводили 26 хворим (2 група). Після лікування в групі 1 рівні офісного систолічного та діастолічного артеріального тиску були на 7.6 % та 6.9 % ($p<0.05$), а середньодобові показники систолічного та діастолічного артеріального тиску (за даними добового моніторингу артеріального тиску) були на 8.6 % та 8.1 % ($p<0.05$) нижчими, ніж в групі 2. У групі 1 були зареєстровані позитивні зміни в обміні ліпідів та вуглеводів. Встановлено, що зниження фактор некрозу пухлин-α в групі 1 було значно вищим (38.6 %, $p<0.05$), ніж в групі 2 (20.6 %, $p<0.05$). Пацієнти 1-ї групи продемонстрували достовірне зниження малонового діальдегіду (Δ-37.5 % проти Δ-15.7 % в групі 2, $p<0.05$) та збільшення активності супероксиддисмутази (Δ30.4 % проти Δ9.0 %, відповідно, $p<0.05$). Таким чином, додавання кверцетину пацієнтам з артеріальною гіпертензією та метаболічним синдромом підвищує ефективність антигіпертензивної терапії, позитивно впливає на глюкометаболічні параметри, рівні фактору некрозу пухлин-α та антиоксидантний статус у плазмі крові.

Ключові слова: артеріальна гіпертензія, метаболічний синдром, перекисне окислення ліпідів, фактор некрозу пухлин-α, кверцетин.

The work is a fragment of the research project "Development of methods for early diagnosis and drug prevention of fibrosing processes in patients with comborbid pathology (hypertension and type 2 diabetes mellitus) based on the assessment of cardiohemodynamics and renal function", state registration No. 0120U102062.

One of the important medical and social problems of our time is the problem of arterial hypertension (AH), which is due to its high prevalence and the fact that AH is one of the main risk factors for cardiovascular diseases and their complications and mortality [5]. It is known that AH together with abdominal obesity, disorders of carbohydrate and lipid metabolism is included in the concept of metabolic syndrome (MS) [1, 13]. The significance of studying MS is associated with its high prevalence, the risk of developing cardiovascular complications and premature death [10]. According to the data of the International Diabetes Federation [6] up to 20–25 % of the world population of adults have MS, while among children and young adults the frequency of this condition is steadily increasing, which is obviously associated with an increase in the prevalence of obesity. Prevention, early detection and treatment of MS are an important medical and social problem of modern medicine.

In clinical practice, various methods of treating AH in patients with MS are used [3, 2]. At the same time there are no generally accepted methods of treating this patient population that can reduce the progression of target organ damage. Therefore, expanding the arsenal of highly effective and safe methods of treating patients with hypertension and MS, aimed at increasing the effectiveness of drug therapy, is an actual task of practical medicine.

In recent years, the inflammatory and regulatory mechanisms involved in the onset and progression of MS have been actively studied. According to the results of numerous studies, a relationship was revealed between MS, as well as its various components and the level of circulating pro-inflammatory markers [9]. The negative influence of MS components on the elastic properties of arteries has been established [7]. In addition, the key link between hyperglycemia and vascular changes is oxidative stress – increased production of free radicals (superoxide anion radical, hydroperoxide radical, hydroxide radical, hydrogen peroxide and hypochlorous acid), accompanied by activation of nitric oxide, lipid peroxidation, intensification expression of adhesion molecules, increased tendency to thrombosis and oxidative damage to proteins and DNA [12]. Therefore, the treatment optimization of patients with AH in combination with MS, taking into account the identified clinical features in this category of patients, remains actual.

Quercetin (3, 3', 4', 5, 7-pentahydroxyflavone) is one of the most common flavonoids with multimodal effects. It has been proven that the antioxidant activity, anti-inflammatory, antimutagenic, immunomodulatory properties of quercetin are related to the pharmacological effects [14]. A pronounced therapeutic potential of the drug has been demonstrated for cardiovascular diseases, diabetes mellitus and its complications and other diseases [10]. However, the effect of quercitin in the treatment of patients with AH and MS remains insufficiently studied.

The purpose of research was to increase the effectiveness of the therapy of the patients with arterial hypertension and metabolic syndrome.

Materials and methods. 56 patients were examined (29 males and 27 females, mean age 54.7±3.5 years) with stage II, grade 2 AH and MS, who did not undergo constant antihypertensive therapy. All patients were investigated in accordance with the recommendations of the European Society for Hypertension and the European Society of Cardiology (ESH/ESC, 2018). MS was diagnosed according to the Metabolic Syndrome Consensus (2009). Informed consent was obtained from all patients to participate in the study. All patients had an abdominal obesity type. In addition, the body mass index (BMI) and the ratio of the waist circumference / hip circumference (WC/HC) were determined. Obesity (BMI ≥30 kg/m^2) was observed in 30 (53.6 %) patients and 26 (46.4 %) had overweight (BMI ≥25 kg/m^2).

The control group consisted of 20 practically healthy volunteers (9 males and 11 females, mean age 54.5±3.3 years).

All examined persons underwent general clinical examination, anthropometric measurements, office blood pressure (BP) were measured, clinical analyses of blood were made, fasting blood serum (FBS), levels of glycosylated hemoglobin (HbA1c) in whole blood, insulin, lipid profile indices (total cholesterol – TC, low density lipoprotein cholesterol – LDL-C, high density lipoprotein cholesterol – HDL-C, triglycerides - TGs) were determined, insulin resistance was evaluated by the HOMA-IR index.. All laboratory and instrumental studies were carried out in "National Institute of Therapy named after L.T. Malaya of the National Academy of Medical Sciences of Ukraine".

Daily blood pressure monitoring (DBPM) was performed using "ABPM-02" equipment (Meditech, Hungary). The following parameters were determined: daytime, nighttime, average daily (24 hours) systolic (SBP) and diastolic (DBP) BP, heart rate; indicators of "pressure load" – the time index (TI) of BP separately for SBP and DBP during day and night hours.

The content of malonic dialdehyde (MDA) was determined by the reaction with thiobarbituric acid (TBA), which at high temperature (100°C) in an acidic medium proceeds with the formation of a colored trimethyl complex. Superoxide dismutase (SOD) activity was determined by the level of inhibition of nitrotetrazolium blue reduction by the enzyme with the participation of reduced nicotinamide adenine dinucleotide (NADH) and phenazine metasulfate. The concentration of tumor necrosis factor-α (TNF-α) was determined in the blood serum using enzyme immunoassay with employment of using a commercial test system from DRG, (USA).

After registration of the initial data, 30 patients of the main group (group 1) were prescribed basic antihypertensive therapy (combination of lisinopril, amlodipine in individually selected doses) and quercetin medication ("Quertin", "Borshagivskiy KhFZ", Ukraine) at a dose of 40 mg three times a day during 2 months. The comparison group (group 2) consisted of 26 patients who were prescribed basic therapy for AH. Patients in both groups also received statins and antithrombotic therapy. Titration and dose correction of the drugs were carried out if necessary at the 2nd and 4th weeks of the study until the target BP level was achieved. Re- investigation was carried out after 2 months of treatment.

Mathematical computer processing of the research results was carried out using the "Statistica 8.0" software package (StatSoft Inc, USA). The mean (M), variance, standard deviation, median (m), significance, and significance level (p) were calculated. Differences were considered significant at the level of statistical significance $p<0.05$. To assess the relationship between the parameters the method of

correlation analysis was used with the calculation of Pearson's correlation coefficients (with a normal distribution) and Spearman (with a distribution that differs from normal).

Results of the study and their discussion. After the course of treatment the analysis of the dynamics of blood pressure according to the data of office measurements and DBPM of patients with AH and MS showed a high antihypertensive efficiency of combination therapy with the addition of quercetin (tables 1, 2).

Table 1

Dynamics of office blood pressure during treatment of patients with arterial hypertension and metabolic syndrome (M±m)

Variables	Group	Initial	After treatment
Office SBP, mm Hg	1 (n=30)	156.7±3.7	128.0±3.3*
	2 (n=26)	155.8±3.8	137.8±3.1*
Office DBP, mm Hg	1 (n=30)	95.1±2.3	78.6±1.6*
	2 (n=26)	95.3±2.5*	84.1±1.8*

Note: * – reliability of differences in comparison with the initial data ($p < 0.01$).

It was found that after the course in the main group, the levels of office SBP and DBP were 7.6 % and 6.9 % ($p<0.05$) lower than in the comparison group.

Table 2

Dynamics of daily blood pressure monitoring parameters during treatment of patients with arterial hypertension and metabolic syndrome (M±m)

Variables	Group	Initial	After treatment
SBP (24), mm Hg	1 (n=30)	146.3±3.5	123.8±2.3***
	2 (n=26)	145.6±3.6	134.5±2.5**
SBP (D), mm Hg	1 (n=30)	147.5±3.8	122.3±2.6***
	2 (n=26)	148.7±3.9	136.6±2.8**
SBP (N), mm Hg	1 (n=30)	137.8±3.5	119.1±2.3***
	2 (n=26)	138.5±3.8	128.1±2.1*
DBP (24), mm Hg	1 (n=30)	94.6±2.6	78.9±2.3***
	2 (n=26)	94.3±2.5	85.3±2.1**
DBP (D), mm Hg	1 (n=30)	92.4±3.8	79.5±3.3***
	2 (n=26)	93.7±3.5	84.8±3.2*
DBP (N), mm Hg	1 (n=30)	87.6±3.6	75.0±2.5***
	2 (n=26)	87.1±3.2	79.8±2.5*
TI SBP (D), %	1 (n=30)	65.1±5.1	21.3±2.8*
	2 (n=26)	64.9±5.3	27.9±2.9*
TI SBP (N), %	1 (n=30)	50.9±5.3	16.1±3.1**
	2 (n=26)	51.3 ± 5.8	23.5±3.4**
TI DBP (D), %	1 (n=30)	50.5±8.5	13.8±3.1**
	2 (n=26)	51.3±8.3	23.3±3.3**
TI DBP (N), %	1 (n=30)	43.8±7.3	15.3±4.3**
	2 (n=26)	44.1±7.6	21.5±4.7**

Notes: * – reliability of differences in comparison with the initial data, $p<0.05$; ** – $p<0.001$. Abbreviations: SBP (24) – average SBP over 24 hours; SBP (D) – average SBP SAD per day; SBP (N) – average SBP per night; DBP (24) – average DBP in 24 hours; DBP (D) – average DBP per day; DBP (N) – average DBP per night; TI – the time index of BP.

Analysis of DBPM parameters after 8 weeks of therapy revealed a high antihypertensive efficacy of both treatment regimens (table 2), but more pronounced with the addition of quercetin. Thus, the average daily SBP and DBP were 8.6 % and 8.1 % ($p<0.05$) less in patients of group 1 compared with group 2. In all patients after treatment with the addition of quercetin pressure load parameters (TI of hypertension in SBP and DBP) significantly decreased at all time intervals, but did not exceed the norm, which testified about a stable 24-hour antihypertensive effect. After the course of treatment the values of the pressure load parameters of the TI SBP and DBP significantly decreased in both groups of patients. At the same time a greater decrease in pressure load was observed in patients of the main group (table 2).

After the therapy, a favorable dynamics of lipid and carbohydrate metabolism parameters was observed (table 3).

Table 3

Changes in biochemical parameters in the dynamics of treatment of patients with arterial hypertension and metabolic syndrome (M±m)

Variables	Group	Initial	After treatment
TC, mmol/L	1 (n=30)	5.63±0.36	4.46±0.29*
	2 (n=26)	5.69±0.29	5.02±0.18
HDL-C, mmol/L	1 (n=30)	3.09±0.25	2.39±0.09*
	2 (n=26)	3.07±0.22	2.63±0.08
HDL-C, mmol/L	1 (n=30)	1.01±0.05	1.20±0.03*
	2 (n=26)	1.02±0.06	1.10±0.04
TG, mmol/L	1 (n=30)	2.03±0.05	1.65±0.04*
	2 (n=26)	2.02±0.05	1.87±0.06
FBS, mmol/L	1 (n=30)	5.38±0.26	4.59±0.23*
	2 (n=26)	5.37±0.26	5.32±0.22
TNF-α, pg/mL	1 (n=30)	14.21±0.59	8.73±0.55*
	2 (n =26)	14.25±0.58	11.31±0.56*

Note: * – reliability of differences in comparison with the initial data ($p<0.05$).

Indices of the dynamics of the key pro-inflammatory cytokine - TNF-α, which characterizes the activity of the systemic nonspecific inflammatory response, after the treatment showed a decrease in its values in both groups, but significantly ($p<0.05$) more in the main group (by 38.6 %, $p<0.05$) compared with group 2 (table 3).

Analysis of the effect of therapy on lipid peroxidation (LPO) and the state of the antioxidant status (table 4) showed that in the main group of patients with AH and MS a significantly greater decrease in the content of the secondary product of free radical oxidation – MDA in blood plasma (by 37.5 %, $p<0.05$) was detected with the comparison group. The activity of the key antioxidant enzyme – SOD was determined as an indicator of antioxidant protection. The noted increase in SOD activity by 30.4 % ($p<0.05$) in patients of group 1 shown the activation of the antioxidant defense of the body. In group 2 changes in LPO and antioxidant protection parameters were also significant, but to a significantly ($p<0.05$) lesser degree compared to the main group: a decrease in the MDA level by 15.7 % and an increase in SOD activity by 9.0 %, $p<0.05$).

Table 4

Dynamics of parameters of oxidative stress during treatment with quercetin (M±m)

Variables	Group	Initial	After treatment
MDA, mmol/L	1 (n=30)	7.68±0.46	4.8±0.41*
	2 (n=26)	7.62±0.41	6.42±0.45*
SOD erythroc., %	1 (n=30)	37.8±1.9	49.3±1.8*
	2 (n=26)	37.5±1.2	40.9±1.0*

Note: * – reliability of differences in comparison with the initial data ($p<0.05$).

Therefore, combination therapy with the addition of quercetin had a positive effect on both the oxidative and antioxidant systems, which was manifested in the inhibition of LPO and activation of compensatory processes, which normally provided the containment of free radicals at a level necessary to ensure normal metabolic processes in the cell.

The treatment with the investigational drugs was characterized well tolerance. Side effects and adverse events were not registered during the observation period.

It was found that in patients with AH and obesity there is a deterioration in the elastic properties of the arterial wall with the development of remodeling of the cardiovascular system as a result of activation of carbonyl and oxidative stress processes, chronic subclinical inflammation, endothelial dysfunction, activation of atherogenic factors at the initial stage of atherogenesis, which leads to acceleration subclinical atherosclerosis [8]. It has been shown that changes in the lipid profile in patients with AH and obesity are characterized by an increase in its atherogenic fractions and increases with an increase in the degree of obesity [11]. The relationship between the components of MS, the severity of metabolic disorders, and the level of proinflammatory cytokines has been demonstrated, that confirms the role of systemic inflammation in the pathogenesis of MS and in the mechanism of damage to target organs such as the myocardium and the vascular wall. In addition, free radical reactions play an important role in the etiology and pathogenesis of AH in patients with MS. Therefore, the possibility of using drugs in therapeutic regimens that can affect the parameters of chronic inflammation and oxidative stress in patients with AH and MS, attracts the attention of researchers.

The data of experimental and clinical studies support the effectiveness of quercetin in various areas of clinical medicine (allergiology, immunology, endocrinology, gastroenterology, oncology, etc.) [4]. The antioxidant potential of the flavonoid quercetin, which protects the brain, heart and other tissues from damage due to ischemia and reperfusion the influence of toxins and other factors leading to oxidative stress, has been proven [10]. The dose-dependent antihypertensive effect of quercetin has been experimentally established. At the same time, other pharmacological properties of the drug have not been studied enough.

Our data demonstrated that the addition of quercetin to the treatment regimen for patients with AH and MS increased the effectiveness of antihypertensive therapy and improved daily BP profiles. These data are consistent with previous studies by other authors [10]. It is assumed that this effect may be due to the influence of quercetin on endothelial function, as evidenced by a decrease in the content of endothelin-1 in the blood of patients with AH [4].

Systemic inflammation is characterized by certain violations of the biochemical and cellular composition of the blood and reflects pro-inflammatory changes, which are manifested by the accumulation in the blood of not only chemokines and cytokines – inflammatory mediators, dissolved forms of their receptors, but also adhesion molecules, activation of cellular elements – monocytes, leukocytes, lymphocytes, platelets, the development of systemic oxidative stress. It has been established that the development of chronic subclinical inflammation in obese patients promotes the progression of metabolic disorders and the formation of hypertension [7]. It has been noted that TNF-α promotes the progression of atherosclerotic lesions of the vascular wall, including by blocking the ability of endothelial cells to produce nitric oxide in response to insulin stimulation [13]. In our study, the antioxidant properties of quercetin were confirmed according to the dynamics of the MDA level and SOD activity in patients with AH and MS. This corresponded to a positive effect on the parameters of lipid and carbohydrate metabolism, as well as a decrease in the content of TNF-α in the blood in both groups, which was more pronounced ($p < 0.05$) in the group that additionally received quercetin.

Conclusion

Thus, combination therapy with the addition of quercetin in patients with AH and MS increased the effectiveness of antihypertensive therapy, realized an additional pathogenetically necessary effect on glucometabolic parameters (a significant decrease in the level of total cholesterol, LDL-C, TG and an increase in HDL-C, decrease in FBS), a decrease in chronic systemic inflammation according to data pro-inflammatory cytokine – TNF-α, and also showed a more pronounced antioxidant effect.

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Стаття надійшла 26.03.2020 р.