КВЕРЦЕТИН, ЯК ПОТЕНЦІЙНИЙ ТЕРАПЕВТИЧНИЙ ЗАСІБ ПРИ ГІПЕРТОНІЧНІЙ ХВОРОБІ, УСКЛАДНЕНІЙ ДИСПЛАЗІЄЮ СПОЛУЧНОЇ ТКАНИНИ

QUERCETIN AS A POTENTIAL THERAPEUTIC AGENT IN HYPERTENSION COMPLICATED BY CONNECTIVE TISSUE DYSPLASIA

Юрій Федоров (Yuriy Fedorov), доктор медичних наук, професор, Львівський медичний університет, Україна (Doctor of Medical Sciences, Professor, Lviv Medical University, Ukraine)
Альона Ковпак (Alona Kovpak), кандидат фармацевтичних наук, доцент, Львівський медичний університет, Україна, (PhD in Pharmaceutical Sciences, Associate Professor, Lviv Medical University, Ukraine)
Володимир Пиндус (Volodymyr Pyndus), кандидат медичних наук, доцент, Львівський медичний університет, Україна (PhD in Medical Sciences, Associate Professor, Lviv Medical University, Ukraine)
Сергій Голота (Sergiy Golota), кандидат фармацевтичних наук, доцент, Львівський медичний університет, Україна (PhD in Pharmaceutical Sciences, Associate Professor, Lviv Medical University, Ukraine)
Corresponding author: Volodymyr Pyndus

Анотація. В даній статті наведено узагальнені дані щодо впливу кверцетину під час лікування артеріальної гіпертензії, ускладненої дисплазією сполучної тканини. В даний час проводяться численні дослідження з вивчення ролі різних генів у розвитку артеріальної гіпертензії. Одним із факторів ризику АГ, який залишається недостатньо вивченим, є патологія колагену – недиференційована дисплазія сполучної тканини (НДСТ). Наявність сполучної тканини в усіх органах і системах, її спільне походження з мезенхімою, гладкою мускулатурою, кров'ю та лімфою призводить до диспластичних змін у будь-якому органі та системі. Серед багатьох метаболічних засобів у лікуванні АГ у поєднанні з ДСТ найбільшої уваги заслуговує біофлавоноїд кверцетин, який має виражену антиоксидантну дію. Застосування водорозчинного кверцетину в комплексній терапії хворих на АГ у поєднанні з ДСТ знижує частоту рецидивів гіпертонічних кризів у післягоспітальному періоді, зменшує кількість ускладнень, призводить до зниження стабілізації крові, тиску, додатковий гіпотензивний ефект.
Ключові слова: гіпертензія, захворювання серцево-судинної системи, захворювання системи кровообігу, кверцетин.

Abstract. This article summarizes data on the effect of quercetin during the treatment of arterial hypertension, complicated by connective tissue dysplasia. Currently, numerous studies are being conducted to study the role of various genes in the development of arterial hypertension. One of the risk factors for hypertension, which remains insufficiently studied, is collagen pathology - undifferentiated connective tissue dysplasia (UND). The presence of connective tissue in all organs and systems, its common origin with mesenchyme, smooth muscle, blood, and lymph leads to dysplastic changes in any organ and system. Among the many metabolic agents in the treatment of hypertension in combination with DST, the bioflavonoid quercetin, which has a pronounced antioxidant effect, deserves the most attention. The use of water-soluble quercetin in the complex therapy of patients with hypertension in combination with DST reduces the frequency of recurrence of hypertensive crises in the post-hospital period, reduces the number of complications, leads to a decrease in blood stabilization, pressure, additional hypotensive effect.
Keywords: hypertension, diseases of the cardiovascular system, diseases of the circulatory system, quercetin.

Introduction. Hypertension is the most common cardiovascular disease in the world [1, 2]. In Ukraine, hypertension ranks first in the structure of prevalence among diseases of the circulatory system in the adult population. In 2016, the number of patients with hypertension in Ukraine reached 10 million 421 thousand [3]. Currently,

numerous studies are being conducted to study the role of various genes in the development of hypertension [4]. One of the risk factors for hypertension, which remains insufficiently studied, is collagen pathology – undifferentiated connective tissue dysplasia (NDST) [5]. The presence of connective tissue in all organs and systems, its common origin with mesenchyme, smooth muscle, blood, and lymph leads to dysplastic changes in any organ and system [6, 7]. NDST is characterized by changes in collagen, elastic fibrils, glycoproteins, proteoglycans, and fibroblasts, which are based on hereditary mutations of genes that encode the synthesis and spatial organization of collagen, structural proteins, protein-carbohydrate complexes, mutations of genes, enzymes, and their cofactors [8]. When diagnosing and treating hypertension combined with DST, it is necessary to take into account not only the blood pressure level, but also the presence of concomitant risk factors [9], under the influence of which its total value can significantly increase. It is extremely important to study the effects of new, mainly metabolic, and pro-inflammatory factors of cardiovascular risk, as well as the search for metabolic disorders characteristic of hypertension combined with DST and their drug correction [10, 11].

Among many metabolic agents in the treatment of hypertension combined with DST, bioflavonoid quercetin, which has a pronounced antioxidant effect, deserves the most attention. Quercetin exhibits the properties of modulators of the activity of various enzymes involved in the degradation of phospholipids (phospholipases, phosphogenases, cyclooxygenases), which affect free-radical processes and are responsible for the biosynthesis in cells of nitrogen oxide, proteinases, etc. Quercetin increases the level of nitric oxide in endothelial cells, which explains its cardioprotective effect in ischemic and reperfusion injury of the myocardium. It also exhibits antioxidant and immunomodulatory properties, reduces the production of cytotoxic superoxidanion, normalizes the activation of the subpopulation composition of lymphocytes, lowers their activation level, affects lipid metabolism, acute phase reactions, and reduces the level of uric acid in the blood of patients.

The purpose of the study is to improve the effectiveness of treatment of patients with arterial hypertension (AH) combined with undifferentiated connective tissue dysplasia (UND), using metabolic therapy.

Material and methods. An examination of 52 patients (19 women and 33 men) with stage II-III hypertension with manifestations of NDST, who were undergoing inpatient treatment in the cardiology department of the Chernivtsi Medical Center, was conducted. The average age of the patients was 61.14±2.58 years. Patients with hypertension combined with NDST, depending on the treatment, were divided into two groups: Group I consisted of 30 patients who received generally accepted therapy, and Group II (22 people), who, in addition to basic therapy, received metabolic medical means corvitin (water-soluble quercetin) in a dose of 0.5 g, previously diluted in 50 ml of physiological solution twice a day for 5 days, followed by the use of chewable tablets of quercetin 40 mg 1 tab. 3 times a day for a month. The control group consisted of 15 practically healthy people. The study was conducted twice: when the patient was admitted to the hospital, on the day of discharge (on the 12th-14th day of treatment). Patients with neoplasms, renal, hepatic, and respiratory insufficiency were not included in the examination. Patients were examined, palpated, percussed, and auscultated.

Determination of total cholesterol and lipid fractions was carried out using the enzyme method on the FP-900 analyzer (Finland), to study the level of CRP, seromucoid, the latex turbidimetric method was used, and the determination of uric acid (UC) was carried out by the colorimetric enzyme method on the Gobas 6000 analyzer using the test system of Roche Diagnostics (Switzerland) in the KMK laboratory LSHMD (Chernivtsi city). Instrumental research methods were carried out with the help of: ECG, echocardiography, DMAT, ultrasound of internal organs and vessels of the lower extremities, ultrasound duplex examination of the carotid and vertebral arteries, radiological examination of the bone-joint system, consultations of an ophthalmologist, a neurologist, a traumatologist, and a dentist.

The detection of external signs of connective tissue dysplasia (DST) in patients with hypertension was carried out using anthropometric research methods (assessment of body structure, skin condition, muscles, calculation of the Quetelet index, detection of the fate of hostenomelia, flat feet, deformations of the spine and chest, joint hypermobility). The results were evaluated using the table of diagnostic coefficients of DST signs and minor developmental anomalies (according to V.M. Yakovlev et al., 2008). Upon reaching the diagnostic threshold of 21 points, a conclusion was formulated about the presence of DST. Tables of the significance of clinical markers were used to determine the severity of DST (Kaduryna T.M., Abbakumova L.N., 2008). The degree of severity of DST in each patient was determined by the sum of points: mild degree of DST - sum of points < 20, average - 21-40, severe - 41 and more.

To obtain the results of blood pressure indicators during the day, daily monitoring of blood pressure measurement by the oscillometric method ABRM 50 (NEACO, London) was used. Blood pressure readings were recorded every 15 minutes. during the active period of the day (day) and every 30 minutes. in the passive period (night). The target average daily blood pressure level was considered to be less than 130/85 mm Hg. Art. (during the day less than 140/80 mm Hg, at night less than 120/80 mm Hg) and/or reduction of SBP/DAP by 10/5 mm Hg. Art. and more.

Statistical processing of the results was carried out using Microsoft Office Excel 2007 and "Statistica 10.0". The reliability of the results was assessed using non-parametric statistics and Student's t-test. The difference in indicators was considered reliable with $p<0.05$.

The study is a fragment of research works of Lviv Medical Institute LLC on the topic of "Improving the system of circulation of drugs during pharmacotherapy on the basis of evidentiary and forensic pharmacy, organization, technology, biopharmacy and pharmaceutical law" (state registration number 0120U105348, implementation period 2021-2026).

Results and discussion. As a result of the study, patients with stage II-III hypertension were diagnosed with NDST of varying degrees of severity. In the 1st group of patients (n=30), DST of moderate degree of severity was detected in 27 (90%), severe degree – in 3 persons (10%). In the II group of patients (n=22), DST of moderate degree of severity was found in 18 (81.8%), severe degree – in 4 patients (18.2%).

When external phenotypic signs were detected in patients with hypertension, the most frequent manifestations of DST were skin striae, which accounted for 60% of patients in the 1st group, 80% of the 2nd group, mild joint hypermobility was observed

in the 1st group – 25 %, II – in 70% of patients. Spine pathology in the form of mild scoliosis was observed in two groups of patients. Other most common external signs of DST were: flat feet, present in the 1st group of patients - 60%, the 2nd - in 81.8% of patients. Appearance patients with hypertension were accompanied by stigmata of dysembryogenesis, including macrodactyly of the first toe in 70% of the first toe group, and 90% of the second toe.

Among the internal signs of NDST in patients with hypertension, the most frequently observed abnormal chords in the ventricles of the heart (AHSHS), which in the 1st group of patients were - 45.45%, II - in 60% of people, which indicates the deficiency of connective tissue of the heart. Eye pathology in the form of retinal angiopathy occurred in 60% of the 1st group, 90% of the 2nd group, gallbladder abnormalities (bends, membranes) in the 1st group of patients – 40%, the 2nd group - in 60% of patients. Congenital malformation of cerebral vessels was observed in 60% of the first and 90.9% of the second type of patients.

After the analysis, it was established that complex treatment of patients with hypertension, combined with DST, with the use of water-soluble quercetin normalizes blood pressure in 92.6% of patients ($p<0.01$), increases tolerance to physical exertion in 80.2 % of cases ($p<0.01$), with basic therapy – 78.2% and 68.2% ($p<0.05$), respectively, on the 14th day of treatment. On the 5th day, headaches and dizziness disappeared in 86.9% of patients, and after 14 days - 96.7% ($p<0.05$). Upon admission to the hospital, an increased heart rate was found in half of the patients in each group. Rapid normalization of the heartbeat was noted only in the group that received the metabolic drug water-soluble quercetin, which has antiarrhythmic and anti-inflammatory effects.

When examining the state of lipid metabolism in patients with hypertension combined with DST, before treatment it was significantly different from the norm in both groups, namely, the level of triglycerides was increased by 33.7% ($p<0.01$), the level of LDL cholesterol was exceeded the indicator of healthy individuals by 27.5% ($p<0.01$), and HDL cholesterol was reduced by 30.9% ($p<0.05$). After 14 days of treatment, significant changes in the parameters of the blood lipid spectrum were noted only in the group of patients who underwent metabolic therapy with the use of water-soluble quercetin, the level of CHD decreased by 24.9% ($p<0.01$), LDL-C by 24.7% ($p<0.05$), and CS

HDL by 25.1% ($p<0.01$) compared to data before treatment. As for CRP and seromucoid, an increase in their level was found in both groups of patients before treatment compared to the indicators of the control group. The level of seromucoid decreased by 37.1% ($p<0.05$), CRP

– by 65.8% ($p<0.001$) compared to the data before treatment. A positive effect was also found in the II group of patients, but the data are not statistically reliable. The SC level in the II group of patients who used complex treatment decreased by 18.8% ($p<0.05$), and in the I group by 12.3% ($p<0.05$).

Conclusions. The use of water-soluble quercetin in the complex therapy of patients with hypertension, combined with dST, reduces the frequency of recurrence of hypertensive crises in the post-hospital period, reduces the number of complications, leads to a reduction in the stabilization of blood pressure, additional hypotensive effect.

Positive dynamics of the clinical picture of the disease and rapid normalization of acute-phase reactions, blood lipid spectrum and uric acid level from the use of complex therapy in patients with hypertension combined with dST are noted.

Prospects for further research. Further research should be focused on the influence of metabolic therapy on the level of pro-inflammatory cytokines taoxyproline in blood in patients with hypertension combined with dST, as one of the factors in the development of cardiovascular complications.

Conflict of interest. The authors confirm that they are the authors of this work and have approved it for publication. The authors also certify that the obtained data and research was conducted in the absence of any commercial or financial relationships that could be interpreted as a potential conflict of interest.

The authors express their gratitude to the Rector of Lviv Medical University, Doctor of Medical Sciences, Professor, Academician of the Academy of Sciences of the Higher School of Ukraine, Honored Worker of Education of Ukraine, Mykhailo Stepanovych Regeda, for his help in preparing the article for publication.

Funding. The authors declare that this study did not receive a specific grant from any funding agency in the public, commercial, or non-commercial sectors.

Data availability statement. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

References.

1. Clinical recommendations on arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) in 2013. *Arterial. Hypertension.* 2013. No. 4 (30). P. 61-157. URL: https://doi.org/10.1093/eurheartj/eht151
2. Huffman M., Lloyd Jones D., Ning H. et al. Quantifying Options for Reducing Coronary Heart Disease Mortality By 2020. *Epidemiology and Prevention*. *Circulat.* 2013. Vol. 127. No. 5. P. 2477-2484. DOI: 10.1161/CIRCULATIONAHA.112.000769
3. Svishchenko E.P., Mishchenko L.A. Clinical and demographic characteristics of patients with newly detected arterial hypertension: results of the START study. *Ukr. cardiol journal*. 2017. No. 6. P. 14-23. URL: https://ucardioj.com.ua/index.php/UJC/article/view/97
4. Tseluiko V.V., Yakovleva L.M. Genetic aspects of arterial hypertension in patients with coronary heart disease. *Arterialny hipertensiya.* 2013. No. 5(31). URL: http://www.mif-ua.com/archive/article/37263
5. Babak O.Ya., Andreeva A.O. Hormonal changes in adipose tissue of patients with hypertension and obesity. *Ukr. therapist journal* . 2013. No. 1. P. 63-67.URL: https://doi.org/10.22141/2224-0721.16.7.2020.219007
6. Williams B., Lacy P., Thom S. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results and the Conduit Artery Function Evaluation (CAFE) study. *Circulat.* 2006. Vol. 113. P. 1213-1225. DOI: 10.1161/circulationaha.105.595496
7. Characterization of cardiovascular risk factors in hypertensive patients receiving dual combination antihypertensive drugs: results from the FACTOR-Duo study.

Ukrainian Journal of Cardiology. 2024. Vol. 31. Iss. 4. P. 23−34. URL: https://doi.org/10.31928/2664-4479-2024.4.2334.
8. Koval S., Penkova M., Mysnychenko O. Changes in the nature of the disease in patients with hypertension and type 2 diabetes — representatives of the civilian population after a long stay in the combat zone. *International journal of endocrinology* 2024. Vol.19. No.8. P. 586–591. URL: https://doi.org/10.22141/2224-0721.19.8.2023.1342
9. Whelton A. Hyperuricemia and hypertension. *Hypertension.* 2012. No.60. P. 1112-1113. URL: https://doi.org/10.1161/HYPERTENSIONAHA.112.198341
10. Zaremba E.Kh., Rak N.O., Mushroom N.V. et al. The relationship between undifferentiated connective tissue dysplasia and arterial hypertension. *Health and society*. 2017. No. 1-2. P. 139-140. URL: https://doi.org/10.22141/2224-0551.12.6.2017.112842
11. Nikolenko V.N, Oganesyan M.V, Vovkogon A.D. et al. Morphological signs of connective tissue dysplasia as predictors of frequent post-exercise musculoskeletal disorders. *BMC Musculoskelet Disord*. 2020. Vol.8. No.21(1). P.660. DOI: 10.1186/s12891-020-03698-0
12. Tsubanova N., Kovpak A., Zamorskyi I. Study of possible sex features of ramipril and candesartan treatment under experimental arterial hypertension in rats. *Ceska Slov Farm.* 2022. Vol.71. No.3. P.116-120. PMID: 36058640 .