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OPTIMIZATION OF COMPLEX THERAPY IN PATIENTS WITH ARTERIAL HYPERTENSION AND THYROTOXIC CARDIOMYOPATHY

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The study included 69 patients with stage II arterial hypertension and moderate and severe thyrotoxicosis with thyrotoxic cardiomyopathy. All patients underwent general clinical, laboratory, and instrumental examinations followed by statistical processing of the obtained results. Patients were divided into control and main groups. Patients in the main group were prescribed quercetin in addition to basic and combined antihypertensive therapy. The results of this study prove that the additional use of quercetin has a reliable positive effect on the morpho-functional state of the heart by reducing the size and volume of the left atrium and ventricle, improving the systolic and diastolic function of the myocardium of the left ventricle and regression of hypertrophy with a decrease in the proportion of concentric hypertrophy. The patients also had a stable decrease in heart rate, a significant decrease in the number of extrasystoles, episodes of atrial fibrillation and their duration, an increase in temporal parameters of heart rate variability with normalization of the ratio of spectral indicators, compared to when using only basic therapy. Quercetin should be used as part of complex therapy for patients with arterial hypertension and thyrotoxicosis, with signs of thyrotoxic cardiomyopathy in order to minimize cardiovascular disorders, prevent the progression of structural and functional remodeling of the heart and the occurrence of arrhythmic complications.

Keywords: arterial hypertension, thyrotoxicosis, thyrotoxic cardiomyopathy, quercetin.

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ОПТИМІЗАЦІЯ КОМПЛЕКСНОЇ ТЕРАПІЇ У ПАЦІЄНТІВ З АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ І ТИРЕОТОКСИЧНОЮ КАРДІОМІОПАТІЄЮ

Нами обстежено 69 пацієнтів з тиреотоксикозом та артеріальною гіпертензією II стадії, які були розподілені на контрольну і основну групи. Хворим основної групи до базисної терапії тиреостатиком і комбінованої антигіпертензивної терапії додатково призначався кверцитин. Всім пацієнтам до і наприкінці лікування проводились загальноклінічні, інструментальні і лабораторні дослідження з подальшою стастичною обробкою результатів. Результати даного дослідження демонструють, що додаткове застосування кверцетину чинить достовірний позитивний вплив на морфо-функціональний стан серцево-судинної системи шляхом зменшення розмірів і об'ємів лівого передсердя і шлуночка, покращення систолічної і діастолічної функції міокарда та регресу гіпертрофії лівого шлуночка зі зменшенням частки концентричної гіпертрофії. Також у хворих відмічалось стабільне зниження частоти серцевих скорочень, достовірне зменшення загальної кількості екстрасистол, епізодів фібриляції передсердь і їх тривалості, підвищення часових показників з нормалізацією співвідношення спектральних показників варіабельності серцевого ритму, ніж при застосуванні тільки базисної терапії. Кверцетин доцільно застосовувати у складі комплексної терапії хворим на артеріальну гіпертензію і тиреотоксикоз із ознаками тиреотоксичної кардіоміопатії з метою мінімізації серцево-судинних порушень, попередження прогресування структурно-функціональної перебудови серця і виникнення аритмічних ускладнень.

Ключові слова: артеріальна гіпертензія, тиреотоксикоз, тиреотоксична кардіоміопатія, кверцетин.

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Thyrotoxicosis (TT) is a syndrome in which there are manifestations of persistent excessive levels of thyroid hormones in the blood, regardless of the cause of the increase in their levels [13]. The prevalence of thyrotoxicosis is 0.8 % in Europe and 1.3 % in the United States [15], with a predominance among women.

Cardiovascular system (CVS) lesions in the long-term course of TT are the earliest and most clinically significant and affect the further prognosis and quality of life of these patients [14]. Through both direct and indirect effects of excess thyroid hormones, there is a direct toxic effect on the myocardium, changes in the sensitivity of the CVS to catecholamines, and the development of systolic arterial hypertension (AH) [6]. Myocardial contractility increases, which contributes to an increase in pulse pressure, but diastolic pressure decreases, and a hyperkinetic type of circulation is formed against the background of vasodilation [9]. Clinically, these disorders are manifested in the form of hypertension, tachycardia both at rest and during exercise, rhythm and conduction disorders, among which atrial fibrillation (AF) and extrasystoles (ES) prevail [8, 11].

One of the most dangerous cardiovascular lesions in patients with TT is thyrotoxic cardiomyopathy (CM). It represents the final stage of formation of changes in left ventricular (LV) remodeling and function

in case of untimely diagnosis and/or inadequate treatment of TT. CM is the initial manifestation of hyperthyroidism in only 6 % of patients, although less than 1 % develop severe LV dysfunction with a decrease in ejection fraction and heart failure [10].

The basic conservative therapy of patients with TT is based on the use of thyroid-stimulating drugs and beta-blockers [8]. Along with thyro-static therapy, patients with AH and TT are traditionally prescribed antihypertensive drugs, among which beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers occupy a prominent place [7].

However, there is an urgent need to optimize approaches to the treatment of patients with AH and TT in the setting of thyrotoxic CM. The use of metabolic therapy in the complex treatment, in particular, corvitin/quercetin drugs, can be considered as one of the promising areas [2]. Quercetin is a plant-derived flavonoid that modulates the activity of phospholipase enzymes, lipoprotein lipase, phosphogenases involved in the degradation of phospholipids, and proatherogenic lipoproteins. The drug has a powerful anti-inflammatory effect, inhibiting 5-lipoxygenase, cyclooxygenase, hyaluronidase, calcium-dependent ATPase, leukotriene synthesis, and has anti-ischemic, antioxidant, membrane-stabilizing, and antitoxic properties as well [12].

The purpose of this study was to investigate the efficacy and direct effect of corvitin/quercetin (quercetin and povidone complex) on the course of thyrotoxic cardiomyopathy as part of complex therapy in patients with arterial hypertension and thyrotoxicosis.

Materials and methods. All patients underwent general clinical, instrumental (Doppler echocardiographic examination, Ambulatory blood pressure monitoring (ABPM), Holter ECG monitoring (HM ECG)), laboratory (determination of thyroid hormone levels) researches.

The structural and functional state of the CCC was studied on an ultrasound scanner En Visor C (Philips, USA). We determined LV end-systolic (LVEDS) and end-diastolic (LVEDD) dimensions, shortening fraction (FS), end-systolic (LVESV) and end-diastolic (LVEDV) volumes, stroke volume, and LV ejection fraction (LVEF). We also evaluated left atrial (LA) size, interventricular septal thickness (IVSd), and LV posterior wall thickness (PWTd). In the pulse mode, the maximum blood flow velocity in the phase of early LV filling (Em), in the phase of atrial systole (Am) and their ratio (Em/Am) were determined. LV mass (LVM), LV mass index (LVMI), and LV geometry type were determined according to the recommendations of the American Society of Echocardiography (ASE). The criteria for LV hypertrophy (LVH) was taken as LVIM more than 102 g/m^2 for men and 88 g/m^2 for women.

ABPM was performed using the VAT 41–2 apparatus (IKS-TECHNO, Ukraine) according to the standard method.

HM ECG was performed using the SDM 23 system (IKS-TECHNO, Ukraine). We analyzed the time (standard deviation of NN intervals (SDNN), standard deviation of the difference of consecutive NN intervals (rMSSD)) and spectral parameters (power in the low frequency range (LF), power in the high frequency range (HF), LF and HF in normalized units, LF/HF ratio (LF/HF) of heart rate (HR) variability (HRV).

Statistical analysis of the obtained results were performed on a personal computer using the STATISTICA 6.0 and MS Excel XP. The Shapiro-Wilk test was used to assess the compliance of quantitative indicators with the normal distribution. Quantitative indicators with a normal distribution were described as arithmetic means (M) with standard deviation (SD) and 95 % confidence interval (95 % CI) limits. Categorical data were described in terms of absolute values and percentages. The groups were compared by quantitative indicators with a normal distribution, provided that the variances were equal, using the Student's t-test.

The study included 69 patients with stage II AH and TT, including 56 (81.2 %) women and 13 (18.8 %) men. The average age of patients was 53.7±0.4 years, the duration of AH was 4.9±0.6 years, and the duration of TT was 5.8±0.5 years.

According to the goal of the study, two groups were formed: group I control (n=33) – patients received basic therapy (tiamazole 30 mg/day, Lugol's solution 25–30 drops 2–3 times a day, metoprolol 50-100 mg/day and telmisartan 40-80 mg/day); group II main (n=36) – patients were prescribed corvitin in addition to basic therapy: 1.0 g of quercetin and povidone complex with a dilution of 50.0 ml of isotonic sodium chloride solution intravenously drip 2 times a day for 14 days, followed by oral quercetin 2.0 g twice a day for 3 months. A second course of treatment with corvitin/quercetin was performed 3 months later.

The study adheres to the principles of the Helsinki Declaration on Research Involving Human Subjects.

Results of the study and their discussion. Metabolic therapy with corvitin/quercetin in patients of group II resulted in more positive dynamics of intracardiac hemodynamics and LV remodeling compared with the corresponding results of group I, p<0.05 (Table 1).

Table 1

Dynamics of indexes of morphofunctional state of the heart in patients with AH and TT

Index	Group I, (n=33)		Group II, (n=36)	
	Before treatment	After treatment	Before treatment	After treatment
LA, cm	4.06±0.14	3.54±0.09*	4.07±0.11	3.11±0.08*,#
IVSd, cm	1.20±0.04	1.02±0.03*	1.23±0.04	0.95±0.03*,#
PWTd, cm	1.19±0.03	1.01±0.03*	1.22±0.04	0.90±0.02*,#
LVEDS, cm	3.64±0.09	3.13±0.06*	3.66±0.08	2.88±0.05*,#
LVEDD, cm	5.22±0.11	4.71±0.11*	5.27±0.13	4.42±0.09*,#
LVESV, ml	47.85±4.03	39.99±3.58*	46.16±3.79	35.19±3.45*,#
LVEDV, ml	142.14±5.33	127.62±5.04*	141.25±5.31	115.27±4.95*,#
LVM, g	255.62±8.21	218.57±7.30	257.42±8.27	207.09±7.10*,#
LVMI, g/m^2	142.77±6.26	120.79±5.18	143.64±6.47	115.42±5.08*
LVEF, %	58.25±0.93	63.30±0.95	57.34±0.94	64.44±0.96*,#
Em/Am	0.92±0.05	1.22±0.05*	0.84±0.04	1.37±0.05*,#

Notes: 1. * – difference is significant compared to the corresponding index at the beginning of treatment, p<0.05; 2. # – difference is significant compared to the corresponding index of group I, p<0.05.

According to the data obtained, in patients with AH and TT, the use of corvitin/quercetin as part of complex treatment contributed to a more pronounced regression of LVH compared with patients taking only basic therapy (LVM and LVMI decreased by 19.6 % vs. 15.5 % in group I, respectively, p<0.05). In patients of group II, a significant decrease in the percentage of unfavorable types of LV geometry was also recorded, in particular, the proportion of concentric LV was halved (from 72.2 % to 36.1 %, p<0.05).

The reduction in IVSd and PWTd under quercetin therapy was more significant compared with the corresponding values in the use of baseline treatment alone (23.6 % vs. 15.0 % in group I and 25.4 % vs. 15.1 % in group I, respectively, p<0.05). After treatment in group II, a significant reduction in the size (LVEDS by 21.3 % vs. 14.0 % and LVEDD by 16.1 % vs. 9.8 % in group I, respectively, p<0.05) and volumes of the LV (LVESV by 23.8 % vs. 16.4 % and LVEDV by 18.4 % vs. 10.9 % in group I, respectively, p<0.05) and LA (by 23.6 % vs. 12.8 % in group I, p<0.05) than in the control group. These positive changes led to an improvement in systolic (LVEF increased by 12.3 % vs. 8.7 % in group I, p<0.05) and diastolic LV function (Em/Am ratio increased by 63.1 % vs. 32.6 % in group, p<0.05) after complex treatment.

The results obtained indicate that in patients with AH and TT and thyrotoxic CM, additional administration of corvitin/quercetin significantly improves LV systolic and diastolic function and allows achieving a more significant regression of LVH compared with baseline therapy.

The analysis of HM ECG parameters also showed a significant difference between the parameters of groups I and II. The additional prescription of corvitin/quercetin led to a more significant decrease in the average daily HR in group II (by 54.1 % vs. 39.3 % in group I, p<0.05), a decrease in the total number of ES (by 77.7 % and 41.6 %, p<0.05), AF episodes (by 73.9 % vs. 25.8 % in group I, p<0.05) and their duration (by 79.6 % vs. 38.3 % in group I, p<0.05) than in the control group.

When corvitin/quercetin was prescribed, there was an increase in time and decrease in spectral HRV parameters in patients with AH and TT (Table 2).

Table 2

Dynamics of HRV time and spectral parameters in the examined persons

Logarithmic indexes, (Ln)	Group I (n=32)		Group II (n=33)	
	Before treatment	After treatment	Before treatment	After treatment
SDNN, ms	54.48±16.41	63.27±15.16	55.43±15.37	72.55±15.46
rMSSD, ms	22.5±4.02	25.91±4.24	21.82±3.71	26.99±3.88
LF, u. n.	2.69±0.16	2.34±0.14*	2.78±0.16	2.26±0.13*
HF, u. n.	1.06±0.13	1.1±0.13	1.05±0.11	1.15±0.12
LF/HF, u. n.	2.65±0.26	2.11±0.24	2.70±0.23	1.97±0.20*

Notes: * – difference is significant compared to the corresponding indexes at the beginning of treatment, p<0.05

SDNN increased by 30.9 % vs. 16.1 %, RMSSD – by 25.5 % vs. 15.9 % and LF decreased by 23,7 % vs. 13.0 % in the control group, which led to a reliable decrease in the LF/HF ratio at the end of treatment in the main group (by 27.0 % vs. 20.4 % in the control group, $p>0.05$).

Thus, metabolic therapy with corvitin/quercetin contributed to a more significant increase in HRV time and a decrease in the LF/HF ratio than the use of basic drugs alone, which is explained by both the direct effect of corvitin/quercetin on the myocardium and the decrease in sympathetic nervous system activation with its use.

According to the results of ABPM, it was found that in group II the degree of reduction of mean daily systolic (SBP) and diastolic (DBP) blood pressure (respectively, by 22.4 % and 12.7 % from the baseline, $p<0.05$), daytime SBP and DBP (respectively, by 26.1 % and 14.6 % from the baseline, $p<0.05$), nighttime SBP and DBP (by 15.8 % and 13.2 % from baseline, respectively, $p<0.05$), as well as their variability, exceeded the corresponding results of control group I, but this difference between the groups was statistically insignificant ($p>0.05$). At the meanwhile, HR in patients of group II decreased by 52.5 %, which was significantly higher than in patients of group I (by 36.8 %).

In moreover, under the influence of corvitin/quercetin treatment, normalization of the daily blood pressure rhythm was observed in patients of group II (SBP – in 19 patients (52.8 %) versus 12 patients (36.4 %) in group I, DBP – in 12 patients (33.3 %) versus 7 patients (21.2 %) in group I, $p>0.05$). The most significant change was in the number of patients with a “hyper-dipper” type of daily profile (decreased by 53.3 % in group II versus 38.5 % in group I, $p>0.05$).

Thus, the use of corvitin/quercetin in the complex therapy of patients with AH and TT with thyrotoxic CM did not reveal a reliable additional antihypertensive effect, but it showed an undeniably positive effect on the dynamics of AMBP indicators and diurnal blood pressure, a significant reduction in HR in these patients as a powerful risk factor for the development of cardiovascular disease and overall mortality.

A number of other scientific studies have demonstrated a similar effect of quercetin on the state of the CVS and other indicators in various pathological conditions. Thus, the use of quercetin in the complex therapy of patients with myocardial infarction and liver dysfunction led to a significantly faster normalization of systolic and diastolic myocardial function and a decrease in clinical and laboratory manifestations of cytolytic and cholestatic syndromes due to the antioxidant and membrane-stabilizing effects of the drug [5].

A clinical trial involving patients with congestive heart failure and LV systolic dysfunction also showed that intravenous injection of quercetin at a course dose of 4.5 g for 5 days reduces the area of necrosis and statistically significantly improves LV systolic function [2].

In patients with essential AH with concomitant type 2 diabetes mellitus, the additional assignment of quercitin to glucose-lowering and antihypertensive therapy (AHT) contributed to a significant improvement in LV systolic and diastolic function, a significant regression of LVH, and led to a stable decrease in HR with a decrease in the number of ES. At the same time, a positive effect on the time and spectral parameters of HRV and a decrease in urinary albumin excretion by 43.8% in these patients was noted. [3].

The usage of quercetin in combination with antihypertensive drugs (ramipril or candesartan) in spontaneously hypertensive SHR rats demonstrated a positive effect of quercetin on lowering blood pressure, which is due to the pleiotropic effects of quercetin with a protective effect on all indicators of the pro-oxidant antioxidant system [1].

The additional usage of quercetin with basic AHT allowed achieving the target daily, daytime and nighttime SBP and DBP in a sufficiently higher proportion of patients compared to those prescribed AHT alone. Moreover, the endothelioprotective and anti-inflammatory effects of quercetin and a reduction in the risk of heart rhythm disorders have been proven, even against the background of increased concentrations of proinflammatory cytokines and other markers of endothelial dysfunction [4].

Conclusion

The usage of metabolic therapy with corvitin/quercetin as a part of complex treatment (antihypertensive, thyrostatic therapy) in patients with AH and TT against the background of thyrotoxic CM contributed to a significant reduction in wall thickness (IVSd by 23.6 % vs. 15.0 % and PWTd by 25.4 % vs. 15.1 % in the control group, respectively, $p<0.05$), sizes and volumes of the heart cavities (LVEDS by 21.3 % vs. 14.0 %, LVEDD by 16.1 % vs. 9.8 %, LVESV by 23.8 % vs. 16.4 % and LVEDV by 18.4 % vs. 10.9 % in group I, respectively, $p<0.05$), LA by 23.6 % vs. 12.8 % in group I, $p<0.05$), improvement of systolic (LVEF increased by 12.3 % vs. 8.7 % in the control group, $p<0.05$) and diastolic

LV function (Em/Am ratio increased by 63.1 % vs. 32.6 % in the control group, $p<0.05$), significant regression of LVH (LVM and LVMI decreased by 19.6 % vs. 15.5 % in the control group, respectively, $p<0.05$) with a decrease in the proportion of unfavorable types of cardiac remodeling.

Metabolic therapy with corvitin/quercetin in patients with AH, TT and thyrotoxic CM led to a stable reduction in HR (by 54.1 %, $p<0.05$), a reliable decrease in the number of ES, episodes of AF and their duration, as well as significantly increased the temporal and reduced the spectral parameters of HRV and reduced the LF/HF ratio than the use of basic drugs alone.

Patients with AH combined with TT with signs of thyrotoxic CM should be prescribed corvitin/quercetin in addition to the recommended combined antihypertensive and thyroid therapy to minimize cardiovascular disorders, prevent the progression of structural and functional cardiac remodeling and the occurrence of arrhythmic complications.

References

1. Marushchak A, Rohovyi Yu, Savchuk T. Zminy prookysno-antyoksydantnoi systemy u shchuriv serii SHR pry likuvanni hipotenzyvnymy preparatamy (ramiprylom i kandesartanom) v kombinatsii z korvitynom. Ukrainskyi naukovo-medychnyi molodizhnyi zhurnal. 2020;115(1):27–36. doi: 10.32345/USMYJ.1(115).2020.27-36. [In Ukrainian]

2. Parkhomenko AN, Kozhukhov SN. Rezultaty otkrytogo randomizirovannogo issledovaniya po izucheniyu perenosimosti i effektivnosti preparata korvitin u patsientov s zastoynoy serdechnoy nedostatochnostyu i sistolicheskoy disfunktsiey levogo zheludochka. Ukrainskyi medychnyi chasopys. 2014;4(102):71–6. Available from: https://www.umj.com.ua/article/78368. [In Russian]

3. Pastukhova OA. Zastosuvannia kvertsetynu v kompleksnomu likuvanni khvorykh na esentsialnu arterialnu hipertenziyu z suputnim tsukrovym diabetom 2-ho typu. Liky Ukrainy. 2015;2:45–48. [In Ukrainian]

4. Solomenchuk TM, Prokosa MI, Klymkovych OIu. Znyzhennia ryzyku nedosiahnennia kontroliu arterialnoho tysku v patsiientiv z arterialnoiu hipertenziieiu ta ishemichnoiu khvoroboiu sertsia: rol kvertsetynu. Patolohiya. 2023;1(20):14–19. doi: 10.14739/2310-1237.2023.1.268435. [In Ukrainian]

5. Shved NI, Prokopovich EA, Geryak SN, Dobryanskaya VYu. Effektivnost bioflavonoidov i RNK-soderzhaschikh preparatov v kompleksnom lechenii bolnykh infarktom miokarda s narusheniem funktsionalnogo sostoyaniya pecheni. Vrachebnoe delo. 2018;1,2:46–55. doi: 10.31640/JVD.1-2.2018(08). [In Russian]

6. Abdel-Moneim A, Gaber AM, Gouda S, Osama A, Othman SI, Allam G. Relationship of thyroid dysfunction with cardiovascular diseases: updated review on heart failure progression. Hormones (Athens). 2020;19(3):301–309. doi: 10.1007/s42000-020-00208-8.

7. Camm AJ, Lip GYH, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. European Heart Journal. 2012;33(21):2719–47. doi: 10.1093/eurheartj/ehs253.

8. Doubleday AR, Sippel RS. Hyperthyroidism. Gland Surgery. 2020;9(1):124–35. doi: 10.21037/gs.2019.11.01.

9. Khan R, Sikanderkhel S, Gui J, Adeniyi AR, O'Dell K, Erickson M, et al. Thyroid and Cardiovascular Disease: A Focused Review on the Impact of Hyperthyroidism in Heart Failure. Cardiology Research. 2020;11(2):68–75. doi: 10.14740/cr1034.

10. Molinaro G, De Vecchis R, Badolati E, Giannattasio R. Thyrotoxic dilated cardiomyopathy: personal experience and case collection from the literature. Endocrinology Diabetes and Metabolism Case Reports. 2020;24.2020:20-0068. doi: 10.1530/EDM-20-0068.

11. Omotosho YB, Farooqi A, Bakar A, Jeelani H. Thyrotoxicosis: A Primary Cause of Arrhythmias and Acute Heart Failure. Journal of the Endocrine Society. 2021;5(1): A967. doi: 10.1210/jendso/bvab048.1976.

12. Salehi B, Machin L, Monzote L, Sharifi-Rad J, Ezzat SM, Salem MA, et al. Therapeutic Potential of Quercetin: New Insights and Perspectives for Human Health. ACS Omega. 2020;5(20):11849–72. doi: 10.1021/acsomega.Oc01818.

13. Sharma A, Stan MN. Thyrotoxicosis: Diagnosis and Management. Mayo Clinic Proceedings. 2019;94(6):1048–64. doi: 10.1016/j.mayocp.2018.10.011.

14. Vale C, Neves JS, von Hafe M, Borges-Canha M, Leite-Moreira A. The Role of Thyroid Hormones in Heart Failure. Cardiovasc Drugs Ther. 2019;33(2):179–188. doi: 10.1007/s10557-019-06870-4.

15. Wiersinga WM, Poppe KG, Effraimidis G. Hyperthyroidism: aetiology, pathogenesis, diagnosis, management, complications, and prognosis. Lancet Diabetes Endocrinol. 2023;11(4):282–298. doi: 10.1016/S2213-8587(23)00005-0.

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