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EFFICIENCY OF QUERCETIN AND TRIMETASIDINE IN PATIENTS WITH COVID-19 AND CONCOMITANT CHRONIC CORONARY SYNDROME: EFFECT ON SYSTEMIC INFLAMMATION

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Patients with cardiovascular disease suffer a more severe course of COVID-19, requiring enhanced oxygen therapy, including invasive methods, and higher mortality. At the same time, SARS-CoV2 can directly or indirectly adversely affect the course of chronic coronary syndromes, independent of the use of optimal treatment. The use of quercetin in combination with trimetazidine promises new opportunities for the treatment of patients with COVID-19 with concomitant cardiovascular disease, offering an integrated approach to reduce inflammation, oxidative stress, and improve heart muscle function. Quercetin can help reduce symptoms, shorten the duration of the disease and prevent the development of complications, especially in patients with CVD. Trimetazidine, on the other hand, acts as a metabolic modulator of the heart muscle, optimizing oxygen consumption and improving the energy metabolism of cardiomyocytes. In the context of COVID-19, this may help maintain cardiac function in patients with concomitant CVD, reducing the risk of developing heart failure and other complications. The aim of the study was to evaluate the efficacy of quercetin and its combination with trimetazidine compared to standard therapy for the treatment of pneumonia associated with COVID-19 and concomitant chronic coronary syndromes. For the study, 92 patients with COVID-19 and concomitant chronic coronary syndromes were selected and divided into three groups: the first group received only standard treatment (n=31), the second group received additional quercetin intravenously for 7 days (n=29), and the third group received quercetin in combination with trimetazidine for 7 days (n=32). The study of inflammatory markers revealed that the combination of quercetin with trimetazidine reduces inflammatory activity, which is reflected in a decrease in the SIRI and AISI inflammation indices (p<0.001). There was also a decrease in transaminase activity and an improvement in the level of GFR.

Key words: *Covid-19, coronary heart disease, inflammation, quercetin, trimetazidine.*

Connection of the publication with planned research works.

The work was carried out in accordance with the plan of scientific works of Ivano-Frankivsk National Medical University and is a fragment of scientific and research works: «Structural and functional changes of internal organs in chronic non-communicable diseases: possibilities of drug correction» (state registration number 0121U108893), «Changes in internal organs in the long-term period of coronavirus disease, taking into account concomitant pathology» (state registration number 0122U002315).

Introduction.

It is known that cardiovascular disease (CVD) increases the risk of a more severe course of coronavirus disease, causing a greater need for oxygen support, including invasive oxygen support, and higher mortality in such patients. At the same time, the SARS-Cov2 virus directly or indirectly worsens the course of atherosclerotic cardiovascular disease, despite optimal drug therapy. In this context, quercetin and trimetazidine have attracted attention as potential candidates due to their unique properties and widespread use in clinical practice.

Quercetin, known for its pronounced antioxidant and anti-inflammatory properties, may play a significant role in modulating the body's immune response to SARS-CoV-2, reducing oxidative stress and inflammation, which are key factors in the pathogenesis of COVID-19. Studies show that quercetin can help reduce the severity of symptoms, shorten the duration of the disease, and prevent the development of complications, especially in patients with CVD.

Trimetazidine, on the other hand, acts as a metabolic modulator of the heart muscle, optimizing oxygen consumption and improving the energy metabolism of cardiomyocytes. In the context of COVID-19, this may help maintain cardiac function in patients with concomitant CVD, reducing the risk of developing heart failure and other complications.

The combined use of quercetin and trimetazidine may be a promising direction in the treatment of patients with COVID-19 and concomitant CVD, offering a comprehensive approach to reducing inflammation, oxidative stress, and improving the metabolic state of the heart muscle. However, further clinical trials are needed to confirm the efficacy and safety of this therapy.

The aim of the study.

To determine the efficiency of quercetin and the combination of quercetin with trimetazidine compared with baseline therapy in pneumonia associated with COVID-19 and concomitant chronic coronary syndromes (CCS).

Object and research methods.

For the purpose of the study, upon admission to the cardiology department of the Central City Clinical Hospital in Ivano-Frankivsk, the therapeutic department of the Kolomyia Central District Hospital, and the therapeutic department of the Verkhovyna Hospital, 92 patients with COVID-19 were selected, including 49 patients with a history of acute myocardial infarction (MI) and 89 patients with stable angina pectoris. Patients with COVID-19-associated pneumonia were divided into 3 subgroups with different treatment regimens. The first subgroup received only baseline therapy (n=31), the second subgroup received quercetin 0.5 g as an intravenous infusion for 7 days in addition to baseline therapy (n=29), the third subgroup received a combination

of quercetin and trimetazidine at a dose of 80 mg for 7 days in addition to baseline therapy (n=32).

Data were collected from the primary medical records, which include demographic information, anthropometric data, clinical examination results, and laboratory test data.

All patients signed informed consent in accordance with the Declaration of Helsinki.

The body mass index (BMI) was calculated based on body weight and height data using the formula: BMI = body weight / (height)^2.

Pneumonia was verified by chest X-ray and chest computed tomography (CT) scan.

The presence of chronic coronary syndromes was established according to the ESC guidelines for the management and treatment of CCS.

All patients underwent a clinical blood test using a Medonic M-series analyzer (manufactured by Boule, Sweden).

Inflammatory indices were calculated by the following formulas:

Lymphocytes-to-monocytes ratio (LMR) = lymphocytes / monocytes

Neutrophils-to-monocytes ratio (NMR) = neutrophils / monocytes

System inflammation response index (SIRI) = neutrophils * monocytes / lymphocytes

Neutrophils-to-lymphocytes ratio (NLR) = neutrophils / lymphocytes

System immune inflammation index (SII) = neutrophils * platelets / lymphocytes

Platelets-to-lymphocytes ratio (PLR) = platelets / lymphocytes

Aggregate index of systemic inflammation (AISI) = neutrophils * monocytes * platelets / lymphocytes

Derived neutrophils-to-lymphocytes ratio (dNLR) = neutrophils / (leukocytes – neutrophils)

C-reactive protein to leukocytes ratio (CRP/L) = C-reactive protein / leukocytes.

The biochemical blood test was performed using an automatic biochemical analyzer ACCENT MC240 (manufactured by CORMAY, Poland).

Statistical analysis was performed using computer programs Microsoft Excel, MedCalc 22.0, Tibco Statistica 14.0.

The Shapiro-Wilk test was used to test the hypothesis of normal distribution. In case of normal distribution, the arithmetic mean (M) and standard error of the arithmetic mean (m) were determined. In a distribution other than normal, the median and its 25-75 interquartile range (Me [LQ; UQ]) were determined.

Wilcoxon's T-test was used to analyze dependent variables. Frequency (n) and percentage (%) were calculated for qualitative data.

Comparative analysis was performed using the χ^2 test.

To compare three or more independent groups on a common feature, ANOVA (for parametric variables) with Bonferroni post-hoc analysis and Kruskal-Wallis ANOVA (for nonparametric variables) with Dunn post-hoc analysis were performed.

The difference was considered significant at a significance level of $p<0.05$.

Research results.

To evaluate the effect of the study drugs on patients of all groups, demographic, anthropometric and clinical parameters were studied to determine homogeneity. The average age of patients did not differ in the three groups (p=0.96). The gender composition of the groups also did not differ: male patients predominated (p=0.61).

BMI in the three groups did not differ (p=0.39). Although the number of patients with obesity and higher BMI was higher in the first group, there was no statistically significant difference.

The length of hospital stay did not differ (p=0.42) **(table 1)**.

At hospitalization, a slight statistically significant heterogeneity in the studied groups of red blood cell (RBC) counts was found (p=0.045). There was a difference in the number of RBC between the first and third groups: 4.44±0.70 10^{12}/L versus 4.78±0.54 10^{12}/L (p=0.02). No difference was found between the first and second groups (p=0.64), and no difference was found between the second and third groups (p=0.06).

In the group where quercetin and trimetazidine were prescribed in addition to the basic therapy, a decrease in red blood cell count after treatment was found by 5.23% (p=0.007). In other study groups, no significant change in RBC count was observed.

The level of white blood cells (WBC) before treatment did not have a statistically significant difference between the groups (p=0.57). After treatment, there was a tendency to increase the level of WBC, but no statistically significant difference was found (p=0.86).

There was no difference in platelet count at hospitalization in the three groups (p=0.44). There was also no difference after treatment (p=0.93). In the first group (baseline therapy), there was a significant increase in platelet count by 21.30% after treatment (p=0.018). An increase in platelet counts was also detected in the second and third groups but was not statistically significant (p=0.21 and p=0.55, respectively).

There was also no statistically significant difference in erythrocyte sedimentation rate (ESR) levels at hospitalization (p=0.17). After treatment, there was a significant decrease in ESR by 38.90% in the baseline group (p<0.001) and in the group with additional quercetin with trimetazidine – by 39.22% (p=0.002).

In the leukocyte subpopulations at hospitalization, no difference was found between the groups in the level of monocytes (p=0.17), neutrophils (p=0.94) and lymphocytes (p=0.84),

After treatment, a significant increase in the level of monocytes in the first group by 16.13% (p=0.002), a decrease in the level of monocytes in the second group by 13.33% (p=0.005) and a decrease in the third group

Table 1 – Main demographic characteristics of the study groups

Parameter	Group 1 (n=31)	Group 2 (n=29)	Group 3 (n=32)	p
Age, years	66.1±7.4	66.1±9.4	66.9±6.8	0.96
Male sex	22 (70.9%)	18 (62.0%)	19 (59.4%)	0.61
Female sex	9 (29.1%)	11 (38.0%)	13 (40.6%)	0.61
BMI, kg/m^2	29.1±3.4	27.8 [25.4; 31.0]	27.5 [25.8; 30.1]	0.39
Obesity	11 (35.5%)	9 (31.0)	10 (31.2%)	0.56
Length of hospital stay (discharged patients)	15 [10;19]	13 [11; 20]	13 [10; 16]	0.42

Table 2 – Main haematological parameters of the study groups

Value		group 1	group 2	group 3	p
RBC, 10^{12}/L	Before treatment	4.44±0.70	4.51 [4.21; 4.73]	4.78±0.54	0.045
	After treatment	4.48±0.71	4.43 [4.17; 4.74]	4.53±0.49	0.71
	Δ %, p	0.9%, p=0.69	-1.77%, p=0.95	-5.23%, p=0.007	
Hemoglobin, g/L	Before treatment	135.0 [124.0; 147.0]	134.0 [129.0; 144.0]	140.43±17.81	0.43
	After treatment	131.71±19.44	130.68±21.42	134.28±14.36	0.66
	Δ %, p	-2.44%, p=0.54	-2.48%, p=0.42	-4.38%, p=0.005	
WBC, 10^9/L	Before treatment	6.91±2.30	6.50 [4.80; 8.00]	6.85 [5.20; 10.45]	0.57
	After treatment	7.87±2.89	8.32 [5.70; 9.63]	7.80 [6.30; 8.75]	0.86
	Δ %, p	13.89%, p=0.16	28.00%, p=0.10	13.86%, p=0.85	
Platelets, 10^9/L	Before treatment	169.00 [154.00; 233.50]	193.00 [159.00; 225.00]	200.50 [159.50; 244.50]	0.44
	After treatment	205.00 [171.50; 269.00]	219.00 [180.00; 250.00]	216.00 [194.75; 235.50]	0.93
	Δ %, p	21.30%, p=0.018	13.47%, p=0.210	7.73%, p=0.552	
ESR, mm/h	Before treatment	28.25±13.3	17.0 [10.0; 30.0]	24.68±15.15	0.17
	After treatment	17.26±9.46	20.0 [12.0; 25.0]	15.0 [10.0; 19.5]	0.17
	Δ %, p	-38.90%, p<0.001	17.65%, p=0.79	-39.22%, p=0.002	

by 29.41% (p<0.001) was found. When comparing the treatment regimens, a significant difference was found between groups 1 and 2 (0.36 [0.30; 0.40] 10^9/L vs. 0.26 [0.22; 0.30] 10^9/L, p<0.001) and groups 1 and 3 (0.36 [0.30; 0.36 [0.30; 0.40] 10^9/L vs. 0.24 [0.18; 0.26] 10^9/L, p<0.001), but no significant difference was found between treatment regimens 2 and 3 (p=0.065). No difference was found after treatment between the levels of neutrophils (p=0.20) and lymphocytes (p=0.29) in the study groups.

A significant decrease in the level of neutrophils in the groups of additional quercetin administration was found – by 11.57% (p=0.033) and quercetin with trimetazidine – by 18.79% (p=0.004) **(tables 2, 3)**.

Additionally, inflammatory indices were studied to determine the potential of the study drugs to affect systemic inflammation **(table 4, 5)**.

During hospitalization, no significant difference in the value of the LMR index was found between the study groups (p=0.591). At discharge, there was a significant increase in the LMR index by 66.24% (p<0.001) in the group of additional quercetin and trimetazidine. There was also a tendency to increase the LMR index by 35.62% in the second group, but without statistical significance (p=0.063). In the baseline therapy group, there was a decrease in LMR by 23.69% without statistical significance (p=0.163). After treatment, group 1 had a lower LMR than group 2 (3.22 [2.31; 4.48] vs. 5.33 [4.21; 6.83], p=0.002), and LMR was lower than in group 3 (3.22 [2.31; 4.48] vs. 6.45 [5.05; 8.90], p<0.001). There was no significant difference between groups 2 and 3 (p=0.148).

The level of NMR index did not have a statistically significant difference in the subgroups before treatment (p=0.295).

After treatment, there was a significant decrease in the NMR index in group 1 by 16.50% (p=0.036) and an increase by 25.12% in group 3 (p=0.016).

The NMR level was lower in group 1 than in group 2 (15.23 [13.34, 20.82] vs. 21.46 [16.44, 25.54], p=0.008) and lower than in group 3 (15.23 [13.34, 20.82] vs. 23.91 [17.55, 26.23], p<0.001). There was no statistically significant difference between groups 2 and 3 (p=0.338).

The NLR did not differ in the study groups at admission (p=0.222). After treatment, a higher NLR value was observed in the first group than in the third (4.75 [3.66, 6.58] vs. 3.85 [2.81, 4.87], p=0.015). There was no difference between the first and second groups (p=0.08). There was no difference between the second and third groups (p=0.51).

After treatment, there was a significant decrease in the SIRI index by 35.48% in the group of additional quercetin administration (p=0.007) and by 44.59% in the group of additional quercetin administration with trimetazidine (p=0.002). In the first group, there was a 39.34% increase in SIRI, but it was not statistically significant (p=0.06).

The difference between the groups after treatment was significant (p<0.001). Thus, the SIRI index in the first group was higher than in the second (1.70 [1.31, 2.46] vs. 1.00 [0.81, 1.33], p<0.001) and higher than in the third (1.70 [1.31, 2.46] vs. 0.82 [0.51, 1.21], p<0.001). There was no difference between the second and third groups of the study (p=0.263).

SII at the time of hospitalization was (722.42 [612.09; 1091.32] in group 1, (1006.36 [717.41; 1392.45] in group

Table 3 – Main parameters of the leukogram

Value		group 1	group 2	group 3	p
Monocytes, 10^9/L	Before treatment	0.31 [0.26; 0.36]	0.30 [0.25; 0.34]	0.34 [0.28; 0.36]	0.17
	After treatment	0.36 [0.30; 0.40]	0.26 [0.22; 0.30]	0.24 [0.18; 0.26]	<0.001
	Δ %, p	16.13%, p=0.002	-13.33%, p=0.005	-29.41%, p<0.001	
Neutrophils, 10^9/L	Before treatment	6.39 [4.71; 7.33]	6.31 [5.67; 6.97]	6.33 [5.54; 7.00]	0.94
	After treatment	5.43 [5.08; 6.75]	5.58 [4.12; 6.46]	5.14 [4.32; 6.05]	0.20
	Δ %, p	-15.02%, p=0.34	-11.57%, p=0.033	-18.79%, p=0.004	
Lymphocytes, 10^9/L	Before treatment	1.30 [1.01; 1.67]	1.18 [0.84; 1.61]	1.29 [0.95; 1.58]	0.84
	After treatment	1.19 [0.93; 1.56]	1.42 [1.07; 1.69]	1.40 [1.08; 1.77]	0.29
	Δ %, p	-8.46%, p=0.720	20.34%, p=0.390	8.53%, p=0.315	

Table 4 – Characteristics of the level of inflammatory indices in dynamics

Value		group 1	group 2	group 3	p
LMR	Before treatment	4.22 [3.25; 6.18]	3.93 [2.38; 6.86]	3.88 [2.63; 5.18]	0.591
	After treatment	3.22 [2.31; 4.48]	5.33 [4.21; 6.83]	6.45 [5.05; 8.90]	<0.001
	Δ %, p	-23.69%, p=0.163	35.62%, p=0.063	66.24%, p<0.001	
NMR	Before treatment	18.24 [15.98; 24.60]	20.92 [17.73; 25.36]	19.11 [16.47; 23.19]	0.295
	After treatment	15.23 [13.34; 20.82]	21.46 [16.44; 25.54]	23.91 [17.55; 26.23]	<0.001
	Δ %, p	-16.50%, p=0.036	2.58%, p=0.830	25.12%, p=0.016	
NLR	Before treatment	4.01 [3.30; 5.95]	5.04 [3.97; 6.34]	5.03 [3.87; 7.33]	0.222
	After treatment	4.75 [3.66; 6.58]	3.71 [3.08; 5.02]	3.85 [2.81; 4.87]	0.044
	Δ %, p	18.45%, p=0.769	26.39%, p=0.672	-23.46%, p=0.094	

2) and (1132.01 [651.09; 1587.46] in group 3, with no statistically significant difference between the study groups (p=0.051).

Although in the dynamics there was a decrease in SII in the second and third groups by 10.24% and 29.75%, it was not statistically significant (p=0.555 and p=0.16, respectively). Group 1 showed an increase in SII by 41.57%, which was statistically significant (p=0.039). After treatment, the level of SII was (1022.72 [740.97; 1369.73] in group 1, (903.23 [753.06; 1101.98] in group 2, and (795.23 [548.30; 1191.32] in group 3). The difference between all compared groups was not statistically significant (p=0.13).

The level of PLR at the time of hospitalisation in group 1 was (142.00 [99.52; 178.00]), in group 2 – (172.68 [132.42; 194.92]) and (176.02 [103.23; 285.62]) in group 3. There was no significant difference (p=0.18).

The dynamics of 28.15% in group 1 was statistically significant (p=0.041). The dynamics in groups 2 and 3 were not significant (p=0.627 and p=0.469, respectively).

The value of AISI at hospitalisation was: in group 1 (219.60 [174.88;307.02]), in group 2 – (304.54 [204.30;469.18]) and in group 3 (306.47 [209.52;544.08]). A statistically significant difference was found between them (p=0.046). A significant difference was found between groups 1 and 3 (p=0.017), and between groups 1 and 2 the difference was not significant (p=0.076), as well as between groups 2 and 3 (p=0.581).

In the dynamics, there was an increase in AISI by 58.24% in the baseline group (p=0.009), a decrease in AISI by 30.12% in the group of additional quercetin administration (p=0.001) and by 39.35% in the combination of two additional drugs (p=0.004).

When comparing between groups, a significant difference was observed between groups 1 and 2 (374.50 [268.51;487.07]), vs (212.80 [183.80;322.01], p=0.001) and more pronounced between groups 1 and 3 (374.50 [268.51;487.07], vs 212.80 [183.80;322.01], p<0.001).

The CRP/L level before treatment was (3.30 [2.04, 6.51]) in the first group, (3.09 [1.55, 7.82]) in the second group, and (2.96 [2.01, 5.98]) in the third group. No significant differences were found between the subgroups (p=0.74). In the dynamics of all three subgroups, a significant decrease in the CRP/L index was observed: in the first group of patients who received only basic therapy – by 44.54% (p<0.001), in the group receiving additional quercetin – by 43.36% (p=0.006) and in the group receiving additional quercetin with trimetazidine – by 46.28% (p=0.002).

After treatment, there was no statistically significant difference in CRP/L values in the study groups (p=0.90).

There was no statistically significant difference in ALT levels between the groups both before treatment (p=0.61) and after treatment (p=0.22).

At hospitalization, the alanine transaminase (ALT) level was (30.2 [18.8; 37.7]) U/L in subgroup 1, (24.8 [18.9; 42.6]) U/L in subgroup 2, and (24.1 [18.9; 34.0]) U/L in subgroup 3. There was no statistically significant difference in ALT levels between the subgroups (p=0.61).

Also, after treatment, the difference in ALT levels between the subgroups was not significant (p=0.22).

Table 5 – Characteristics of inflammatory indices in the dynamics (continued)

Value		group 1	group 2	group 3	p
SIRI	Before treatment	1.22 [0.95; 1.89]	1.55 [0.93; 1.92]	1.48 [1.10; 2.71]	0.17
	After treatment	1.70 [1.31; 2.46]	1.00 [0.81; 1.33]	0.82 [0.51; 1.21]	<0.001
	Δ %, p	39.34%, p=0.06	-35.48%, p=0.007	-44.59%, p=0.002	
SII	Before treatment	722.42 [612.09; 1091.32]	1006.36 [717.41; 1392.45]	1132.01 [651.09; 1587.46]	0.051
	After treatment	1022.72 [740.97; 1369.73]	903.23 [753.06; 1101.98]	795.23 [548.30; 1191.32]	0.13
	Δ %, p	41.57%, p=0.039	-10.24%, p=0.555	-29.75%, p=0.160	
PLR	Before treatment	142.00 [99.52; 178.00]	172.68 [132.42; 194.92]	176.02 [103.23; 285.62]	0.18
	After treatment	181.98 [134.19; 224.25]	160.77 [135.98; 219.23]	137.39 [111.89; 216.27]	0.45
	Δ %, p	28.15%, p=0.041	-6.89%, p=0.627	-21.95%, p=0.469	
AISI	Before treatment	219.60 [174.88; 307.02]	304.54 [204.30; 469.18]	306.47 [209.52; 544.08]	0.046
	After treatment	374.50 [268.51; 487.07]	212.80 [183.80; 322.01]	185.88 [109.81; 277.06]	<0.001
	Δ %, p	58.24%, p=0.009	-30.12%, p=0.001	-39.35%, p=0.004	
dNLR	Before treatment	1.34 [1.04; 1.75]	1.18 [0.84;1.61]	1.29 [0.95;1.58]	0.62
	After treatment	1.19 [0.93;1.56]	1.42 [1.07;1.69]	1.40 [1.08;1.77]	0.29
	Δ %, p	-11.19%, p=0.326	20.33%, p=0.390	8.53%, p=0.315	
CRP/L	Before treatment	3.30 [2.04; 6.51]	3.09 [1.55; 7.82]	2.96 [2.01; 5.98]	0.74
	After treatment	1.83 [1.16; 2.89]	1.75 [1.12; 2.42]	1.59 [1.17; 3.09]	0.90
	Δ %, p	-44.54%, p<0.001	-43.36%, p=0.006	-46.28%, p=0.002	

In the dynamics, the ALT level significantly decreased in the subgroup receiving BT with quercetin and trimetazidine by 10.79% (p=0.005).

AST levels did not differ between the subgroups (p=0.63) both at baseline and at follow-up (p=0.58).

Similarly to ALT, aspartate transaminase (AST) levels were significantly reduced by 29.04% in the subgroup treated with trimetazidine and quercetin (p<0.001).

There was no statistically significant difference in ALT levels between the groups both before treatment (p=0.61) and after treatment (p=0.22).As for the glucose level, at the beginning of treatment, the value was 6.56 [6.13; 7.55] mmol/l in group 1, (6.98 [6.53; 7.73]) mmol/l in group 2, and (6.96 [6.14; 7.37]) mmol/l in group 3. There was no significant difference between them.

In the dynamics, a significant decrease in glucose levels was observed in all three groups; thus, in the first group, glucose levels decreased by 9.45% (p=0.013), in the second group – by 19.34% (p<0.001), and in group 3 – the most significant decrease in glucose levels by 32.18% (p<0.001).

After treatment, there was a significant difference in glucose levels between the groups (p=0.002).

The level of CRP did not have a statistically significant difference between the study groups at the beginning of treatment (p=0.73). In the dynamics after treatment in all three groups, a significant decrease in CRP levels was observed: by 44.28% in group 1 (p<0.001), by 55.16% in group 2 (p=0.01), and by 41.15% in group 3 (p<0.001). However, there was no difference between them after treatment (p=0.77).

During the treatment, a decrease in creatinine level was detected in all three groups, but it was significant only in group 3 by 8.0% (p=0.03).

In the dynamics, a significant decrease in urea levels was observed in group 1 by 20.81% (p<0.001), in group 2 by 35.59% (p<0.001), and in group 3 by 29.69% (p<0.001).

The difference in urea levels between the groups after treatment was significant (p=0.002). Thus, in the first group, the urea level was significantly higher than in the second group (7.04 [6.28; 7.52] mmol/l vs. 5.81 [5.27; 6.71] mmol/l, p=0.001) and higher than in the third group (7.04 [6.28; 7.52] mmol/l vs. 6.18 [5.33; 6.91] mmol/l, p=0.003), with no significant differences between groups 2 and 3 (p=0.803).

When comparing the groups by estimated glomerular filtration rate (eGFR) at the beginning of treatment, there was no significant difference between them (p=0.08). In group 1, there was a slight increase in eGFR by 3.49% (p=0.20) and in group 2 – by 2.65% (p=0.01), in group 3 the increase in eGFR was the most pronounced – by 24.59% (p<0.001).

After treatment, the most significant difference in eGFR was between the first and third groups (66.99 [62.38; 75.30] ml/min/1.73 m^2 vs. 77.63 [71.59; 81.25] mL/min/1.73m^2, p<0.001), eGFR in the third group was also higher than in the second group (77.63 [71.59; 81.25] mL/min/1.73m^2 vs 71.06 [70.14; 77.04] mL/min/1.73m^2), but without statistical significance (p=0.064). There was no difference between the first and second groups (p=0.137).

Discussion of research results.

Our study investigated the potential anti-inflammatory effect of trimetazidine and quercetin in the context of concomitant CCS in COVID-19-associated pneumonia.

Cheema, H.A., Sohail, A et al. studied the potential benefits of quercetin in the context of COVID-19 treatment and management. Quercetin, a flavonoid found in many fruits and vegetables, has been studied for its effects on patients with COVID-19. Quercetin reduced the risk of intensive care unit admission (RR=0.31; 95% confidence interval (CI) [0.10-0.99]) and the rate of hospitalisation (RR=0.25; 95% CI [0.10-0.62]), but did not reduce the risk of all-cause mortality or the rate of failure to recover. Quercetin may be beneficial for patients with COVID-19, especially when administered in the form of phytosomes, which significantly increases its bioavailability, but large-scale randomised clinical trials (RCTs) are needed to confirm these findings [1].

Research into the potential benefits of quercetin in the treatment and management of COVID-19 continues to show promising results. A study by Di Pierro F, Khan A et al. highlighted the therapeutic potential of quercetin in patients with early-stage COVID-19. This study demonstrated that patients who received quercetin in addition to standard treatment recovered faster compared to those who received standard treatment alone. More patients in the quercetin group tested negative for SARS-CoV-2 after one week and showed a significant reduction in acute symptoms, with COVID-19-related acute symptoms disappearing (p=0.0051). Patients in the quercetin group also demonstrated a significant reduction in mean serum lactate dehydrogenase (LDH) values – from 406.56±183.92 to 257.74±110.73 U/L, p=0.0001 [2].

Further studies of the mechanism of action of quercetin against COVID-19 indicate its anti-inflammatory potential. Studies by Saeedi-Boroujeni, A., Mahmoudian-Sani, MR show that quercetin can modulate various important pathways related to inflammation and immune response, which are crucial in managing the severity of COVID-19, in preventing or mitigating the cytokine storm and acute respiratory distress syndrome (ARDS), which contribute significantly to morbidity and mortality in severe cases [3, 4].

Trimetazidine, an antianginal agent, inhibits β-oxidation of fatty acids by blocking long-chain acetoacetyl-CoA thiolase (thiolase II), which leads to increased glucose oxidation by cardiomyocytes [5]. In addition, TMZ is effective against cardiac fibrosis and ischaemia-reperfusion injury through modulation of cardiac fibroblast activity and the Akt/caspase-3 signalling pathway, respectively [6]. Therefore, trimetazidine may be effective in the treatment of acute coronary syndrome and other ischaemic events in COVID-19 [7]. In addition, fatty acid oxidation inhibitors prevent the entry and replication of SARS-CoV-2 [6]. Thus, TMZ through inhibition of fatty acid β-oxidation may attenuate the pathogenesis of SARS-CoV-2 infection.

Recently, Wu et al. found that trimetazidine is effective against viral myocarditis due to its anti-inflammatory and immunomodulatory effects [8]. Trimetazidine reduces cardiac inflammation in heart failure by inhibiting the release of proinflammatory cytokines interleukin 1 beta (IL-1β), interleukin 6 (IL-6), and tumour necrosis factor alpha (TNF-α) [9].

Conclusions.

The study showed that the use of quercetin with trimetazidine in combination therapy for COVID-19-associated pneumonia and CCS significantly reduced the activity of the inflammatory process, which was manifested by a decrease in the level of inflammatory indices SIRI and AISI. It was also found that this combination reduced the activity of ALT and AST transaminases and increased eGFR.

Prospects for further research.

The problem of selecting the optimal therapy for various comorbid conditions that can complicate the course of COVID-19 is extremely important. CHD is often found among patients with severe COVID-19-associated pneumonia, and research should continue on the selection of treatment that will control the symptoms of CCS and prevent complications that can be caused by SARS-CoV-2. It is also important to monitor patients for fatal and non-fatal cardiovascular events in the long term after recovery from COVID-19.

References

1. Cheema HA, Sohail A, Fatima A, Shahid A, Shahzil M, Ur Rehman ME, et al. Quercetin for the treatment of COVID-19 patients: A systematic review and meta-analysis. Reviews in Medical Virology. 2023 Mar;33(2):e2427. DOI: 10.1002/rmv.2427.
2. Di Pierro F, Khan A, Iqtadar S, Mumtaz SU, Chaudhry MN, Bertuccioli A, et al. Quercetin as a possible complementary agent for early-stage COVID-19: Concluding results of a randomized clinical trial. Frontiers in pharmacology. 2023 Jan 13;13:1096853. DOI: 10.3389/fphar.2022.1096853.
3. Saeedi-Boroujeni A, Mahmoudian-Sani MR. Anti-inflammatory potential of Quercetin in COVID-19 treatment. Journal of Inflammation. 2021 Dec;18:1-9. DOI: 10.1186/s12950-021-00268-6.
4. Derosa G, Maffioli P, D'Angelo A, Di Pierro F. A role for quercetin in coronavirus disease 2019 (COVID-19). Phytotherapy Research. 2021 Mar;35(3):1230-6. DOI: 10.1002/ptr.6887.
5. Huang Q, Deng X, Li Y, Sun X, Chen Q, Xie M, et al. Clinical characteristics and drug therapies in patients with the common-type coronavirus disease 2019 in Hunan, China. International journal of clinical pharmacy. 2020 Jun;42:837-45. DOI: 10.1007/s11096-020-01031-2.
6. Williams CG, Jureka AS, Silvas JA, Nicolini AM, Chvatal SA, Carlson-Stevermer J, et al. Inhibitors of VPS34 and fatty-acid metabolism suppress SARS-CoV-2 replication. Cell Rep. 2021 Aug 3;36(5):109479. DOI: 10.1016/j.celrep.2021.109479.
7. Salinas P, Travieso A, Vergara-Uzcategui C, Tirado-Conte G, Macaya F, Mejía-Rentería H, et al. Clinical profile and 30-day mortality of invasively managed patients with suspected acute coronary syndrome during the COVID-19 outbreak. International Heart Journal. 2021 Mar 30;62(2):274-81. DOI: 10.1536/ihj.20-574.
8. Wu K, Deng D, Yu B, Han Z, Huang L, He Y, et al. Evaluation of the efficacy and safety of Chinese herbal injection combined with trimetazidine for viral myocarditis: a network meta-analysis. Frontiers in Pharmacology. 2021 Apr 29;12:630896. DOI: 10.3389/fphar.2021.630896.
9. Shu H, Peng Y, Hang W, Zhou N. Trimetazidine in heart failure. Frontiers in Pharmacology. 2021 Jan 12;11:569132. DOI: 10.3389/fphar.2020.569132.

ЕФЕКТИВНІСТЬ ЗАСТОСУВАННЯ КВЕРЦЕТИНУ ТА ТРИМЕТАЗИДИНУ У ПАЦІЄНТІВ З COVID-19 ТА СУПУТНІМИ ХРОНІЧНИМИ КОРОНАРНИМИ СИНДРОМАМИ: ВПЛИВ НА СИСТЕМНЕ ЗАПАЛЕННЯ

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Резюме. Серцево-судинні захворювання підвищують ризик тяжчого перебігу коронавірусної хвороби, обумовлюючи більшу потребу в кисневій підтримці, у тому числі – інвазивній, вищу летальність таких пацієнтів. Поряд з цим, вірус SARS-Cov2 прямо чи опосередковано погіршує перебіг атеросклеротичних серцево-судинних недуг, незважаючи на оптимальну медикаментозну терапію. Спільне застосування кверцетину та триметазидину може стати перспективним напрямком у лікуванні пацієнтів з COVID-19 та супутніми ХССЗ, пропонуючи комплексний підхід до зменшення запалення, оксидативного стресу та покращення метаболічного стану серцевого м'яза.

Метою дослідження є визначення ефективності застосування кверцетину та комбінації кверцетину з триметазидином у порівнянні з базовою терапією при пневмонії, асоційованій з COVID-19 та фоновими хронічними коронарними синдромами.

Об'єкт і методи. Відібрано 92 пацієнти, хворі на COVID-19-асоційовану пневмонію з супутніми хронічними коронарними синдромами (ХКС), які розподілені на 3 групи. Перша група отримувала тільки базову терапію (n=31), друга група отримувала в доповнення до базової терапії кверцетин 0,5 г у вигляді внутрішньовенної інфузії впродовж 7 днів (n=29), третя група отримувала додатково до базової терапії комбінацію кверцетину та триметазидину у дозі 80 мг впродовж 7 днів (n=32). Пацієнтам проводився загальний аналіз крові та згідно з його результатами обчислювалися запальні індекси.

Результати. Застосування кверцетину з триметазидином у комбінованій терапії при COVID-19 асоційованій пневмонії та ХКС достовірно знижувало активність запального процесу, яке проявилося зниженням рівня запальних індексів. Після лікування виявилося достовірне зниження індексу SIRI на 35,48% у групі додаткового призначення кверцетину (p=0,007) та на 44,59% у групі додаткового призначення кверцетину з триметазидином (p=0,002). В динаміці спостерігалося підвищення AISI на 58,24% у групі базової терапії (p=0,009), зниження AISI на 30,12% у групі додаткового призначення кверцетину (p=0,001) та на 39,35% – при поєднанні двох додаткових ліків (p=0,004). Також виявлено, що вказана комбінація знижувала активність трансаміназ, динаміці достовірно знизився рівень АЛТ у підгрупі, що отримувала БТ з кверцетином та триметазидином на 10,79% (p=0,005), рівень АСТ мав достовірне зниження на 29,04% у підгрупі, якій призначено триметазидин та кверцетин (p<0,001), також спостерігалося підвищення рШКФ на 24,59% (p<0,001).

Висновки. Проведене дослідження показало, що застосування кверцетину з триметазидином у комбінованій терапії при COVID-19 асоційованій пневмонії та ХКС достовірно знижувало активність запального процесу, яке проявилося зниженням рівня запальних індексів SIRI та AISI. Також виявлено, що вказана комбінація знижувала активність трансаміназ АЛАТ, АСАТ та підвищувала рШКФ, що вказує на безпечність застосування кверцетину та триметазидину у комбінованій терапії.

Ключові слова: Covid-19, ішемічна хвороба серця, запалення, кверцетин, триметазидин

EFFICIENCY OF QUERCETIN AND TRIMETASIDINE IN PATIENTS WITH COVID-19 AND CONCOMITANT CHRONIC CORONARY SYNDROME: EFFECT ON SYSTEMIC INFLAMMATION

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Abstract. Cardiovascular diseases increase the risk of severe coronavirus disease, causing a greater need for oxygen support, including invasive oxygen support, and higher mortality in such patients. At the same time, the SARS-Cov2 virus directly or indirectly worsens the course of atherosclerotic cardiovascular disease, despite optimal drug therapy. The combined use of quercetin and trimetazidine may be a promising direction in the treatment of patients with COVID-19 and concomitant CVD, offering a comprehensive approach to reducing inflammation, oxidative stress and improving the metabolic state of the heart muscle.

The aim of the study was to determine the efficacy of quercetin and the combination of quercetin and trimetazidine in comparison with baseline therapy in pneumonia associated with COVID-19 and background chronic coronary syndromes.

Object and methods. We selected 92 patients with COVID-19-associated pneumonia and concomitant chronic coronary syndromes (CCS), who were divided into 3 groups. The first group received only baseline therapy (n=31), the second group received quercetin 0.5 g as an intravenous infusion for 7 days in addition to baseline therapy (n=29), and the third group received a combination of quercetin and trimetazidine at a dose of 80 mg for 7 days in addition to baseline therapy (n=32). Patients underwent a complete blood count and inflammatory indices were calculated based on its results.

Results. The use of quercetin with trimetazidine in combination therapy for COVID-19-associated pneumonia and CCS significantly reduced the activity of the inflammatory process, which was manifested by a decrease in the level of inflammatory indices. After treatment, there was a significant decrease in the SIRI index by 35.48% in the group of additional quercetin administration (p=0.007) and by 44.59% in the group of additional quercetin administration with trimetazidine (p=0.002). In the dynamics, there was an increase in AISI by 58.24% in the baseline group (p=0.009), a decrease in AISI by 30.12% in the group of additional quercetin (p=0.001) and by 39.35% in the combination of two additional drugs (p=0.004). It was also found that this combination reduced the activity of transaminases, and ALT levels in the subgroup receiving BT with quercetin and trimetazidine significantly decreased by 10, 79% (p=0.005), AST level had a significant decrease by 29.04% in the subgroup prescribed trimetazidine and quercetin (p<0.001), and an increase in GFR by 24.59% (p<0.001) was observed.

Conclusions. The study showed that the use of quercetin with trimetazidine in combination therapy for COVID-19-associated pneumonia and CCS significantly reduced the activity of the inflammatory process, which was manifested by a decrease in the level of inflammatory indices SIRI and AISI. It was also found that this combination reduced the activity of ALT and AST transaminases and increased eGFR, which indicates the safety of quercetin and trimetazidine in combination therapy.

Key words: Covid-19, coronary heart disease, inflammation, quercetin, trimetazidine.

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