ORIGINAL ARTICLE

CONTENTS

Effectiveness of the quercetin use in patients with COVID-19 with concomitant type 2 diabetes mellitus

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ABSTRACT

Aim: To conduct a comparative analysis of the effectiveness of basic therapy and basic therapy with the inclusion of quercetin in patients with COVID-19 with concomitant type 2 diabetes.

Materials and Methods: There were examined 60 patients with COVID-19 with concomitant T2DM. Upon admission into the hospital and again after 10 days, serum levels of interleukin-6, C-reactive protein, procalcitonin, ferritin, endothelin-1 were determined, and capillaroscopy of the nail plate was performed. Patients of the group I (30) against the background of protocol therapy received 0.5 g of quercetin intravenously once a day for 10 days. Patients of the group II (30) received to basic therapy.

Results: After the treatment in patients of the group I general weakness decreased, body temperature normalized, improved saturation indicators, the level of acute-phase parameters (interleukin-6, CRP and ferritin) significantly decreased, a positive effect of quercetin on the level of D-dimer in blood serum was noted, indices of pericapillary edema and hemosiderin deposition significantly decreased, indices diameter of the arterial part of the capillary and capillary network density significantly increased.

Conclusions: The use of quercetin against the background of basic therapy in patients with COVID-19 and concomitant T2DM reliably reduces the level of acute-phase indices, has an important clinical significance for reducing endothelial dysfunction and for preventing thrombotic complications.

KEY WORDS: capillaroscopy, D-dimer, endothelin, respiratory insufficiency

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INTRODUCTION

The problem of coronavirus disease in patients with diabetes mellitus (DM) has become extremely relevant. Predictors of a severe course of the COVID-19 are considered to be the age of 65 years and over, pregnancy, the presence of DM, chronic pathology of the respiratory and cardiovascular systems [1-5]. The course of COVID-19 in patients with DM worsens the results of patients treatment due to the presence of background angiopathy and endothelial dysfunction [6, 7]. The data of many studies indicate the development of endothelial dysfunction as a determining pathological factor of the COVID-19. During capillaroscopy of the nail plate in the acute period of the disease there were noted: the deposition of hemosiderin and microthrombosis, sludge and pericapillary edema [8, 9].

The increased degree of severity of COVID-19 may be related to the chronic inflammation and impaired immune system present in patients with T2DM. Therefore, in our opinion, a combination of antiviral, anti-inflammatory and anti-diabetic therapy will be an effective strategy to combat SARS-CoV-2 infection in patients with type 2 diabetes mellitus [10, 11].

Numerous evidences of the effectiveness of quercetin in reducing the activation of pro-inflammatory cytokines are described in the literature. Quercetin contributes to the restoration of impaired functions of the endothelium through the activation of endothelial NO-synthase, an increase in the contents of NO and prostaglandin F2, and a decrease in endothelin-1 in the blood [11, 12].

AIM

To conduct a comparative analysis of the effectiveness of basic therapy and basic therapy with the inclusion of quercetin in patients with COVID-19 with concomitant type 2 diabetes.

MATERIALS AND METHODS

There were examined 60 patients with the COVID-19 with concomitant T2DM. There were used 60 of

"Medical records of inpatients" (form 003/o) of the Ivano-Frankivsk Regional Clinical Infectious Diseases Hospital, Ukraine, for 2020-2022 years.

Examinations of patients were performed during the first-second days after admission of patients to the hospital and again after 10 days Indicators of treatment effectiveness were body temperature, presence or absence of cough, general weakness, saturation level, length of stay in the hospital, level of ferritin, CRP, procalcitonin, D-dimer and endothelin-1 blood serum, quantitative and qualitative parameters of capillaroscopy.

Capillaroscopy of the nail plate was performed using a digital Capillaroscope 200 Rgt (MEDLA4N Pro), Dino-lite. Capillary network morphometry was performed in the Dino Direct-release_V1/10 program (1). Quantitative morphological parameters were determined: the length of the visible part of the capillary, the diameter of the arterial, venous, transition part of the capillary. Qualitative morphological indices were also studied: dilated capillaries (increased capillary diameter between 20 and 50 μm), giant capillaries (uniformly dilated capillaries with a diameter ≥ 50 μm), microhemorrhages, capillary ramifications, the density of capillaries per linear millimeter (normal density ≥7 capillaries) [9, 13, 14].

All examinations were performed with the consent of the patients, according to the Declaration of Helsinki, 1975 (and its revision of 1983). The research was approved by the commission on bioethics of IFNMU (Expert Decision № 121/21 dated May 13, 2021).

Criteria for the inclusion of patients with coronavirus disease (COVID-19) in study are the presence of confirmation of coronavirus disease (COVID-19) (RNA SARS-COV-2 smear from the naso- and oropharynx) and concomitant type 2 diabetes mellitus, moderately severe and severe course of the disease, age – older than 60 years, and the presence of signed informed consent. Exclusion criteria from the study: the presence of other severe chronic diseases in patients: COPD, bronchial asthma, oncological diseases, lymphoproliferative and onco hematological diseases, HIV-infection, immunodeficiency conditions – congenital, acquired, medically induced, severe chronic heart failure.

Patients were randomly divided into two groups. Patients of the main group I (30) received 0.5 g of quercetin intravenously once a day during 10 days against the background of basic therapy. Patients of the control group II (30) were prescribed basic therapy medicines: antiviral drugs (remdesivir), infusion (detoxification) agents, nonsteroidal anti-inflammatory drugs, anticoagulants, antibacterial agents for appropriate indications, oxygen therapy.

Statistical analysis of data was performed using the Microsoft Excel Statistical Package for Microsoft 365 MSO (setup 2311 of version 16.0.17029.20068) (32-bit version). License ID: EWW_58cc64b2-cc32-48b6-bd4b-cce379e20247_574357c00167ce3139.

The results obtained during the research are represented in the form of absolute numbers or proportions (for the analysis of categorical data) and average values and their errors (for the analysis of quantitative data). The values were calculated according to standard formulas. To analyze the difference between the compared results of various groups or the results before and after the treatment, the parametric Student's criterion and the non-parametric Pearson's test were used (calculation and analysis of the results were performed according to standard methods; the results were considered reliable in the p-value less than 0.05).

RESULTS

As a result of the performed research, it was determined that there were 33 male patients – 55%, 27 female patients – 45%; the age of the patients ranged from 60 to 82 years (on average, 66.02±1.29 years). Patients were admitted for the inpatient treatment, on average, during the 5.50±0.20 day of the disease. All patients (100%) had concomitant type 2 diabetes mellitus. 11 people (18.3%) were diagnosed with the COVID-19 of moderate severity, 49 people (81.7%) were diagnosed with severe disease.

Under the influence of treatment, positive dynamics of all clinical symptoms of the disease was observed in both study groups. Specifically, in patients of the main group receiving the medicine quercetin in combination with basic therapy, normalization of body temperature was noted in 96.7% of patients, while in patients of the control group, a decrease in temperature to normal indices was observed in only 76.7% of patients, and another 23.3% of patients had elevated body temperature (non-parametric Pearson's test χ^2= 5.1923, p = 0.023, p<0.05). Complaints about general weakness in the main group bothered another 23.3% of patients, while in the control group – 53.3% (non-parametric Pearson's test χ^2= 5.7109, p = 0.017, p<0.05). Upon admission to the hospital, cough was noted to the same extent in patients of both groups (main group – in 83.3%, control group – in 80% of patients, non-parametric Pearson's test χ^2= 0.111, p = 0.739, p>0.05). After the treatment, cough decreased in 30% of patients in the main group and in 50% of patients in the control group (non-parametric Pearson's test χ^2= 2.5 p = 0.114, p>0.05).

When assessing the length of patients' stay in the inpatient treatment, it was determined that patients in the main group were treated as inpatients 2 days

Table 1. Dynamics of clinical symptoms of the coronavirus disease (COVID-19) in patients with concomitant T2DM under the influence of treatment with the use of quercetin

Symptoms	Main group, n=30		Control group, n=30	
	Before treatment	After treatment	Before treatment	After treatment
Temperature increase	29 (96,7%)	1 (3,3%)	28 (93,3%)	7 (23,3%)
General weakness	26 (86,7%)	7 (23,3%)	27 (90%)	16 (53,3%)
Cough	25 (83,3%)	9 (30%)	24 (80%)	15 (50%)
Duration of inpatient treatment, days	13,77±0,75		16,13±0,79	

Table 2. Qualitative morphological parameters of capillaroscopy in patients with COVID-19 with concomitant T2DM under the influence of treatment with quercetin

Indicators	Main group (n=30)		Control group (n=30)	
	Before treatment	After treatment	Before treatment	After treatment
Dilated capillaries, n (%)	7 (23,3)	5 (16,7)	8 (26,6)	7 (23,3)
Giant capillaries, n (%)	4 (13,3)	3 (10,0)	4 (13,3)	3 (10,0)
Tortuous capillaries, n (%)	19 (63,3)	16 (53,3)	18 (60,0)	16 (53,3)
Dilatation, n (%)	18 (60,0)	17 (56,7)	16 (53,3)	16 (53,3)
Avascular area, n (%)	16 (53,3)	16 (53,3)	15 (50,0)	15 (50,0)
Pericapillary edema, n (%)	29 (96,7)	19 (63,3) *	30 (100)	28 (93,33)
Capillary ramifications, n (%)	8 (25,8)	8 (25,8)	10 (33,3)	10 (33,3)
Bushy capillaries, n (%)	8 (25,8)	8 (25,8)	10 (33,3)	10 (33,3)
Deposition of hemosiderin, n (%)	21 (70,0)	13 (43,3) *	23 (76,7)	20 (66,7)
Microthromboses, n (%)	8 (26,7)	6 (20,0)	7 (23,3)	6 (20)
Microhemorrhages, n (%)	13 (43,3)	11 (36,7)	15 (50,0)	9 (30)

Notes: * - significant difference between the indices of patients before and after the treatment ($p<0.05$).

less compared to patients in the control group, 13.77±0.75 bed days versus 16.13±0.79 bed days (parametric Student's criterion t=2.17, p=0.017, p<0.05) (Table 1).

Analyzing the development of respiratory insufficiency (RI) at the time of hospitalization of patients of the main group in the hospital, RI of the II degree was determined in 10 (33.33%) patients, SpO_2 85% - 89%, RI of the I degree was found in 10 (33.33%) patients, SpO_2 90% - 94%, no signs of respiratory insufficiency of the 0 degree, in 10 (33.33%) people, $SpO_2 \geq 95\%$. Among the persons of the control group when admitted for the treatment of RI of the I degree was observed in 10 (33.33%) patients, RI of the I degree – in 8 (26.67%) patients, 12 (40.0%) people – without signs of RI. Therefore, the distribution of patients according to the degree of development of respiratory failure at the time of hospitalization did not differ in the main and control groups (non-parametric Pearson's test $\chi^2= 0.404$ p = 0.817, p>0.05).

After the treatment the patients of the main group noted a positive dynamics in reducing the manifestations of respiratory insufficiency. In patients with RI of the I degree saturation significantly increased from 92.5±0.37% before the treatment to 96.5±0.27% after the treatment, such patients no longer needed oxygen donation (Student's parametric test t=8.73, p<0.001). In patients who were admitted to the hospital with RI of the II degree, blood oxygen saturation indices have also improved, the changes were reliable: 88.0±0.26% before the treatment and 90.7±0.33% after treatment (p<0.001). In this group, after the treatment with the inclusion of quercetin, RI of the II degree was observed in 3 (10.0%) patients, RI of the I degree – was observed in 7 (23.33%) patients, such patients continued to receive medical support with the help of an oxygen concentrator.

In patients of the control group with RI of the I degree against the background of the received basic treatment, the saturation indices have also improved, the changes were reliable – 92.0±0.42% and 93.10±0.28%, respectively (p<0.05), but 4 (13.33%) patients required supply of oxygen-enriched air through an oxygen concentrator. In patients with RI of the II degree, blood oxygen saturation indices were 87.9±0.43% and 88.80±0.39%, respectively, (p>0.05). In this group RI of

Table 3. Quantitative morphological parameters of capillaroscopy in patients with COVID-19 with concomitant T2DM under the influence of treatment with quercetin, M±m

Indicators	Main group (n=30)		Control group (n=30)	
	Before treatment	After treatment	Before treatment	After treatment
Capillary length (l cap.), μm	289,17±3,20	302,13±3,65*	289,84±3,43	300,51±1,19*
Intercapillary distance, μm	148,62±14,26	112,58±2,59*	149,12±1,89	130,14± 1,93*
Density of capillaries, n /mm	5,63±0,48	6,12±0,13*	5,79±0,18	5,91±0,18
Diameter of the arterial part of the capillary (d art.), μm	8,31±1,93	9,87±0,18*	8,68±0,20	9,0±0,21
Diameter of the venous part of the capillary (d ven.), μm	15,61±1,82	13,93±0,30*	15,44±1,57	14,90± 0,22*
Diameter of the transition part of the capillary (d trans.) μm	18,79±1,68	16,56±0,23*	18,56±0,32	17,78± 0,49*

Notes: * - significant difference between the indices of patients before and after the treatment ($p<0.05$).

the II degree was observed in 5 (16.67%) patients, they continued to receive a donation of high-flow oxygen, RI of the I degree – in 3 (10.0%) patients; such patients continued to receive oxygen support with the help of a concentrator.

As a result of the initial examination of patients with COVID-19 with concomitant T2DM upon admission to the hospital, the increase of the level of acute-phase indices of the inflammatory response (interleukin-6, CRP, procalcitonin, ferritin) compared to normal values.

The level of interleukin-6, CRP, procalcitonin and ferritin in blood serum in patients of the main group was significantly decreased after the treatment, $p<0.05$. In patients of the control group, after the treatment, a significant decrease in the level of procalcitonin was noted ($p<0.05$), other acute inflammatory indices remained elevated.

As a result of the study, the increase of the level of D-dimer in blood serum was found in patients with COVID-19 with concomitant T2DM during hospitalization compared to similar normal values. After the treatment with the use of quercetin, a slight increase in the average level of D-dimer was noted in the main group of patients at 219 ngFEU/ml, while in the control group it significantly increased at 1262 ngFEU/ml. The significant difference between the groups according to this index after the treatment was 1.43-fold ($p<0.1$). Therefore, the results obtained indicate the positive effect of therapy with the use of quercetin in patients of the main group and the negative dynamics of D-dimer contents in patients of the control group.

During the initial determination of the blood serum endothelin level, it was determined that in the group of patients with COVID-19 with concomitant T2DM, it exceeds normal values. After treatment, a positive effect of quercetin on the level of endothelin was noted. In particular, blood serum endothelin values in patients of the main group had a tendency to decrease to 40.69±2.93 ng/ml, and in patients of the control group to 46.23±3.25 ng/ml, but they still exceeded norm indicators.

Primary capillaroscopy of the nail bed in patients with COVID-19 with concomitant T2DM was performed during the second-third day from the moment the patients were admitted to the hospital. Significant changes in some qualitative morphological parameters of capillaroscopy were observed ($p<0.05$) (Table 2).

In particular, studying capillary morphology in the main group revealed high frequencies: capillary branching in 8 (25.8%) patients, bushy capillaries in 8 (25.8%) patients, tortuous capillaries in 19 (63.3%) patients, pericapillary edema in 29 (96.7%) patients, and microhemorrhages in 13 (43.3%) patients (Table 2).

Examining capillaroscopy's qualitative morphological parameters in the control group upon hospital admission showed high frequencies: capillary branching in 10 (33.3%) patients, bushy capillaries in 10 (33.3%) patients, tortuous capillaries in 18 (60.0%) patients, pericapillary edema in 30 (100.0%) patients, and microhemorrhages in 15 (50.0%) patients (Table 2).

During re-examination after the performed treatment with quercetin use, in patients of the main group the indices of pericapillary edema significantly decreased in 19 (63.3%) people (non-parametric Pearson's test $\chi^2= 10.4167$ $p = 0.0012$, $p<0.05$) and manifestations of such microvascular complications as hemosiderin deposition decreased in 13 (43.3%) patients (non-parametric Pearson's test $\chi^2= 4.3439$ $p = 0.0371$, $p<0.05$). In the control group of patients, no significantly reliable ($p>0.05$) decrease in quality indices of capillaroscopy was found after the basic treatment (Table 2).

When studying the quantitative morphological parameters of the capillaries of patients with COVID-19 with concomitant T2DM during the initial examination,

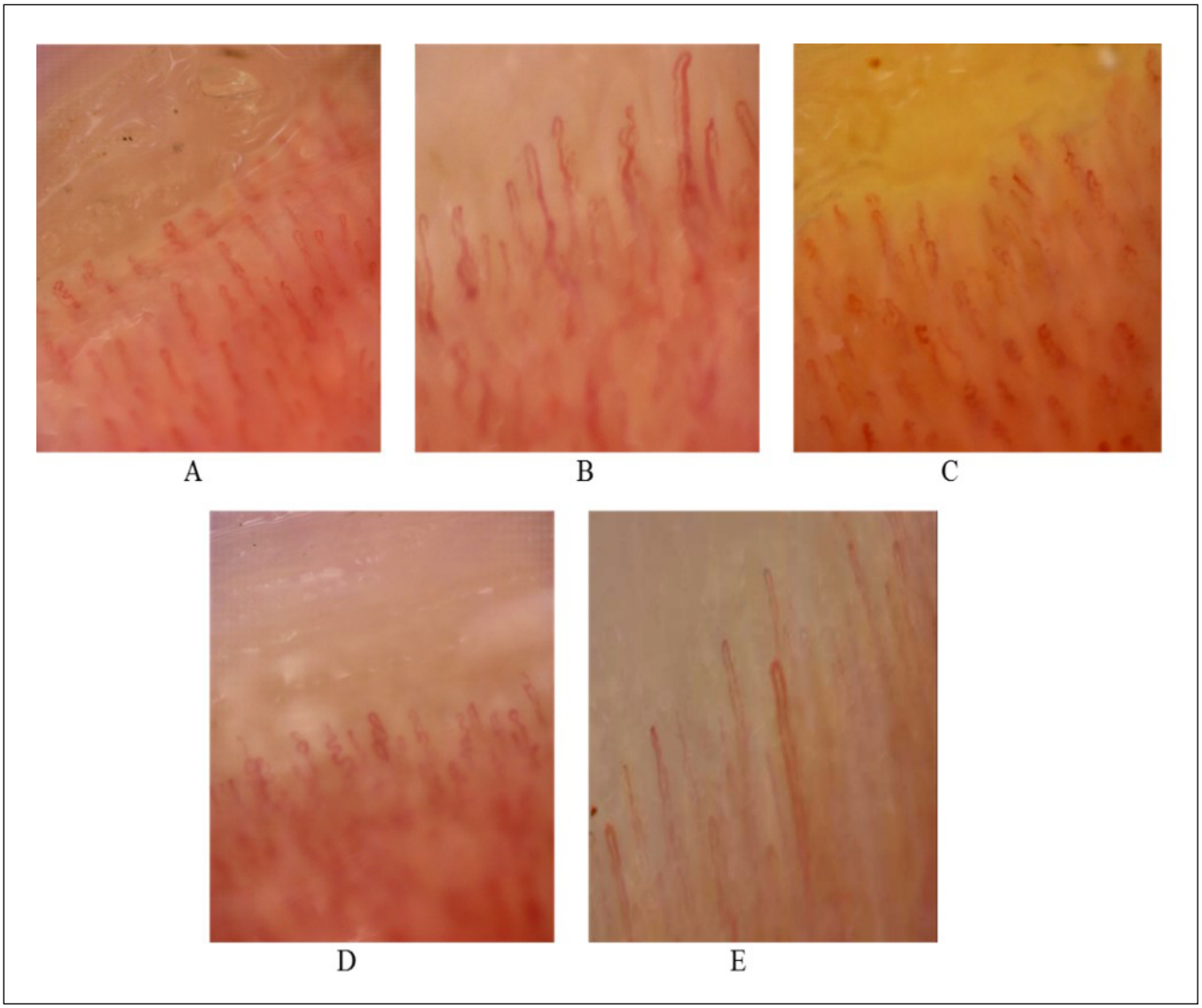

Fig. 1. Nailfold capillaroscopy abnormalities detected in patients with COVID-19 with T2DM (magnification 200×). A) pericapillary edema; B) capillary ectasia; C) microthrombosis; D) tortuous capillaries and microvascular disorders; E) low capillary density.

it was found that in patients of the main group there was a significant decrease in the length of the capillaries, a significant narrowing of the diameter of the arterial and an increase in the diameter of the venous capillary segment, and a significant increase in the diameter of the transitional capillary sections, the density of the capillary network significantly decreased (Table 3).

During re-examination after the treatment with quercetin, the length of the capillaries significantly increased in patients of the main group, the indices of the arterial diameter significantly increased and the indices of the diameter of the venous and transitional sections of the capillary decreased, the density of the capillary network significantly increased. In the control group of patients after the basic treatment, a significant increase in the length of the capillaries was also noted, the indices of the diameter of the venous and transitional sections of the capillary significantly decreased, and the intercapillary distance has significantly decreased. At the same time, in patients of this group, there was no reliably significant increase in the diameter of the arterial section of the capillary and an increase in the density of the capillary network (Table 3).

Representative images of capillary changes in patients diagnosed with COVID-19 with T2DM are represented in the Fig. 1.

DISCUSSION

We've determined in the main group, a positive dynamics was noted in the reduction of manifestations of respiratory insufficiency and increase in saturation in patients with RI of the I and II degrees. Such a reliable improvement in saturation may be due to the membrane-stabilizing,

antioxidant and endothelium-protective effects of quercetin. The results obtained correspond to the data of studies of the other authors [12, 15].

We've also determined a reliable positive effect of quercetin on the level of acute-phase indices, which are the key markers of disease progression and predictors of severity [2, 16, 17]. The data we've obtained, differ from the results published by the authors of the study of the quercetin effectiveness in patients with pneumonia associated with the coronavirus disease (COVID-19), in which there was no statistically confirmed difference between the study groups in terms of CRP and ferritin levels [12].

It should be noted that in our study, high levels of D-dimer in patients with COVID-19 with concomitant T2DM were accompanied by a severe course of the disease, which correlates with data from the literature [2, 18, 19]. Therapy with the use of quercetin had a positive effect (absence of an increase in the level of D-dimer) in patients of the main group. In our opinion, the use of quercetin allows more effective prevention of thrombotic complications of the coronavirus disease (COVID-19). The results obtained by us correspond to the data of studies regarding the effectiveness of quercetin in patients with pneumonia associated with the coronavirus disease (COVID-19) [12]. A positive influence of quercetin on the level of endothelin was also found, which was evidenced by a significant difference between the indices in patients of the main and control groups after the treatment.

Studying the microcirculatory bed in patients with COVID-19 and concomitant T2DM using nail plate capillaroscopy, revealed hemosiderin deposition, common abnormalities were pericapillary edema, capillary dilatation, tortuous and dilated capillaries. The density of the capillary network and the diameter of the arterial section of the capillary were significantly reduced. Such data have been confirmed by a number of scientists [14, 20]. After the treatment with quercetin, pericapillary edema and hemosiderin deposition significantly decreased in patients of the main group, capillary length and diameter indices of the arterial section of the capillary increased. This indicates an improvement in capillary blood flow in patients with COVID-19 with concomitant T2DM under the influence of quercetin treatment.

CONCLUSIONS

1. In patients with COVID-19 with concomitant type 2 diabetes who received quercetin for 10 days against the background of basic therapy, significantly more often, compared to patients in the control group, general weakness decreased (non-parametric Pearson's test χ^2= 5.7109, p = 0.017, p<0.05), body temperature normalized (non-parametric Pearson's test χ^2= 5.1923, p = 0.023, p<0.05), improved saturation indicators (Student's parametric test t=8.73, p<0.001) and the manifestations of respiratory insufficiency decreased, which shortened the length of stay of patients in the hospital by 2 days (parametric Student's criterion t=2.17, p=0.017, p<0.05).
2. The use of quercetin against the background of basic therapy in patients with COVID-19 and concomitant type 2 diabetes significantly reduced the level of acute phase parameters (interleukin-6, CRP and serum ferritin) (p<0.05), the growth of D-dimer level in blood serum slowed down (p<0.1), which reduced the manifestations of endothelial dysfunction, improved qualitative (decreased pericapillary edema and deposition of hemosiderin, p<0.05) and quantitative (increased density of capillaries and diameter of the arterial part of the capillary, p<0.05) parameters of capillaroscopy, and therefore capillary blood flow, in comparison with patients of the control group.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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