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Research Article

Pharmacoepidemiologic and clinical rationale for the inclusion of L-arginine and dihydroquercetin in the combined pharmacotherapy of hypertensive patients with COVID-19

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Abstract

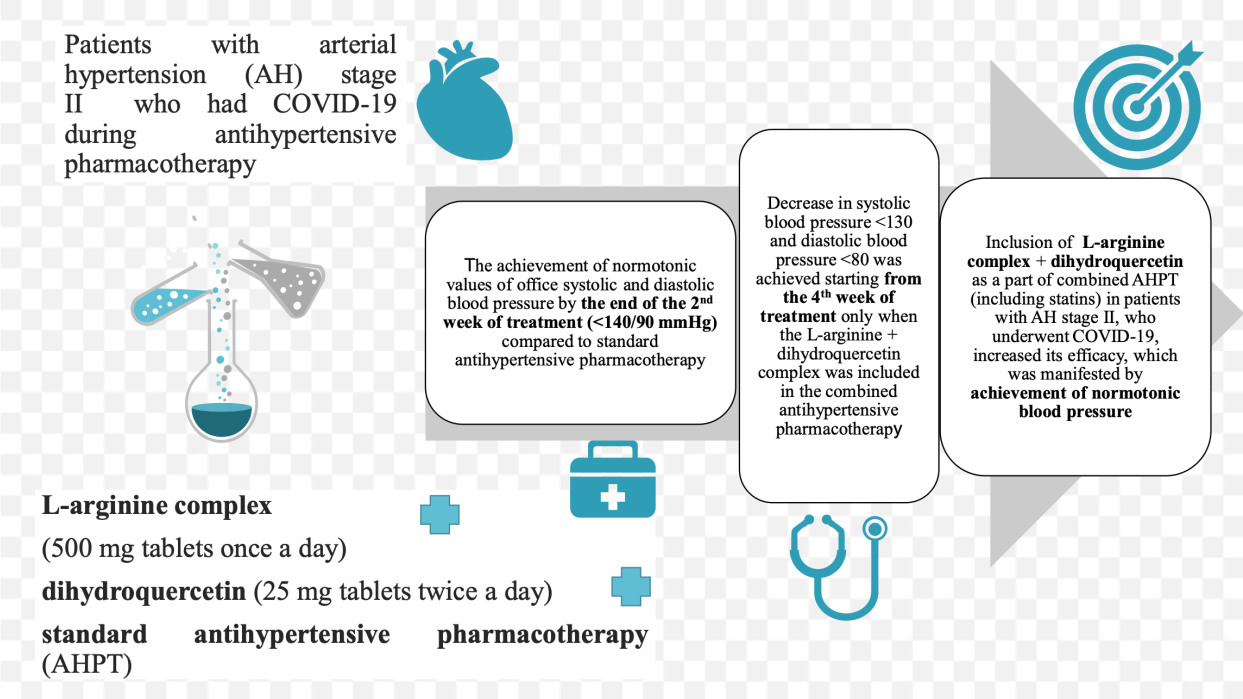
Introduction: The article presents information on the dynamics of office blood pressure in patients with arterial hypertension stage II who have had COVID-19 during antihypertensive pharmacotherapy (AHPT), including the L-arginine complex (500 mg tablets once a day) + dihydroquercetin (25 mg tablets twice a day). **The aim** was to improve the effectiveness of treatment of COVID-19-treated HD patients by pharmacoepidemiologic and clinical substantiation of inclusion of L-arginine + dihydroquercetin complex in the composition of combined AHPT.

Materials and Methods: In order to achieve the goal, we developed a research design, which involved two stages. During the 1st stage, we designed a questionnaire for pharmacy visitors, which in agreement with the management of pharmacies, pharmacists offered visitors to fill out when the latter buy antihypertensive officinal drugs (AHOD). The questionnaire survey of pharmacy visitors in Donetsk was conducted from December 2021 till February 2023. A total of 1118 pharmacy visitors with HD participated in the questionnaire survey. The 2nd stage of the study included HD patients who had undergone COVID-19. Patients who met the inclusion criteria and had no exclusion criteria were included in the study.

Results and Discussion. The proposed treatment has been shown to be more effective than standard antihypertensive pharmacotherapy. This is manifested by the achievement of normotonic values of office systolic and diastolic blood pressure by the end of the 2nd week of treatment (<140/90 mmHg) compared to standard antihypertensive pharmacotherapy, in which this result was achieved only by the end of the 4th week of treatment. A decrease in systolic blood pressure levels to <130 mm Hg and diastolic blood pressure to <80 mm Hg was achieved starting from the 4th week of treatment only when the L-arginine + dihydroquercetin complex was included in the combined antihypertensive pharmacotherapy.

Conclusion: Inclusion of L-arginine complex (500 mg tablets once a day, for 12 weeks according to the 2 weeks-on/1 week-off regimen) + dihydroquercetin (25 mg tablets twice a day, for 12 weeks according to the 4 weeks-on/1 week-off regimen) as a part of combined AHPT (including statins) in patients with stage II HD, who underwent COVID-19, increased its efficacy, which was manifested by achievement of normotonic values of office SAP and DAP (<140/90 mm Hg) by the end of the 2nd week of treatment compared to combined AHPT (including statins) in comparison with combined AHPT (by the end of the 4th week of treatment).

Graphical abstract



Keywords

arterial hypertension, COVID-19, combined antihypertensive pharmacotherapy, L-arginine, dihydroquercetin

Introduction

According to epidemiological studies, the prevalence of arterial hypertension (AH) among adults in economically developed countries of the world is 30-40%. In the age category over 65 years old, this figure reaches 50-65%. In 90-95% of cases, AH is defined as primary (essential, idiopathic) or hypertensive disease (HD) (Naletova 2019).

In March 2020, the World Health Organization (WHO) announced the pandemic of a new coronavirus infection (COVID-19), which was caused by the single-stranded RNA virus SARS-CoV-2. A number of researchers indicate that in severe forms of COVID-19 course there is a statistically significant association between the presence of microthrombi in pulmonary vessels, coagulation balance disorders and vascular endothelial damage (Visseren et al. 2021; Ignatenko et al. 2022). At the same time, the description of COVID-19 pathogenesis, as well as the factors involved in the development of complications of a new coronavirus infection, endothelial dysfunction and ways of its correction are not sufficiently considered.

One of the main markers of endothelial dysfunction is considered to be a decrease in its synthesis of nitric oxide (NO). NO is known to be synthesized from L-arginine in the presence of a number of cofactors and oxygen by various isoforms of NO synthase (NOS); in endothelium, it is endothelial NO synthase (eNOS). In COVID-19, there is a decrease in eNOS expression, which leads to a legitimate decrease in NO synthesis (Zolotovskaya et al. 2022; Dąbrowska and Narkiewicz 2023). As a result, NO-related vasodilatory, anticoagulant, and anti-inflammatory functions of the endothelium are reduced. Disruption of vasodilatory function of endothelium due to its damage will definitely lead to an increase in vascular tone and blood pressure (BP). This circumstance will create a condition for reduction of the effectiveness of treatment, inadequate BP control, which will require correction of antihypertensive pharmacotherapy (AHPT) (Borghi et al. 2022).

HD patients require lifelong therapy to normalize BP. Some antihypertensive officinal drugs (AHODs) have the ability to affect favorably the vascular endothelium, reducing the effects of vascular endothelial damage (Nalyotov et al. 2021). Such AHODs include angiotensin-converting enzyme inhibitors (ACEIs), some β-adrenoblockers (β-AB), in particular nebivolol. At the same time, it is probably insufficient to rely on restoration of endothelial function in COVID-19 patients with HD using only traditional AHODs (Kosmas et al. 2018).

Atherosclerosis, which is caused by lipid metabolism disorder (LM), damages vascular endothelium, thus triggering the processes of AH progression and insufficient efficacy of AHT (Kukharchuk et al. 2020).

Currently, phospholipids, in particular quercetin and dihydroquercetin, are of great importance in the restoration of endothelial function, especially in COVID-19 patients. It was found that quercetin reduces the secretion of proprotein convertase subtilisin/kexin type 9 (PCSK9), which contributes to the reduction of total cholesterol (TCS) and low-density lipoproteins (LDLP) (Shalnova et al. 2022), reversing hypercholesterolemia – one of the leading pathogenetic factors in the development of atherosclerosis leading to the progression of AH (Vorobyov et al. 2020).

Dihydroquercetin, the effect of which on LM is still under study, contains reduced benzopyranol, i.e. it acts as a reducing agent, being an electron donor in free-radical oxidation reactions; i.e. quercetin (containing oxidized benzopyranol) is an oxidized form of bioflavonoid, while dihydroquercetin is a reduced form.

L-arginine, a conditionally essential amino acid, acts as a precursor for the synthesis of many biologically important molecules, but perhaps the most important is nitric oxide (NO), which provides vasodilation. Disruption of NO synthesis or function in the vasculature is one of the most important pathogenetic factors in AH. L-arginine induced enhancement and release of NO production and may improve endothelial function.

The aim was to improve the effectiveness of treatment of COVID-19-treated HD patients by pharmacoepidemiologic and clinical substantiation of inclusion of L-arginine + dihydroquercetin complex in the composition of combined AHPT.

Materials and Methods

Study design

The study was conducted in accordance with the principles of the Declaration of Helsinki. Permission to conduct the study was approved at the meeting of the Ethical Committee of M. Gorky Donetsk State Medical University, Minutes No. 69/5-1 of November 24, 2021.

In order to achieve the goal, we developed a research design, which involved two stages.

During the 1st stage, we designed a questionnaire for pharmacy visitors, which in agreement with the management of pharmacies, pharmacists offered visitors to fill out when when the latter buy AHOD. The questionnaire survey of pharmacy visitors in Donetsk was conducted from December 2021 to February 2023. A total of 1118 pharmacy visitors with HD participated in the questionnaire survey.

Questionnaire survey of respondents allowed identifying gender, age, duration of HD, AHODs taken, and AP level. The survey revealed information about the frequency of visits to the doctor, as well as who prescribed (recommended) AHPT. The questionnaire included information about COVID-19, the period of convalescence, the influence of COVID-19 on AP indices, measures on HD treatment after COVID-19, and also revealed the patients' willingness to participate in a further study.

Based on the results of the questionnaire survey, the frequency of prescription of pharmacological groups as well as individual AHODs was determined. The effectiveness of the conducted treatment was evaluated by the level of systolic AP (SAP) and diastolic AP (DAP).

The 2nd stage of the study included HD patients who had undergone COVID-19. Patients who met the inclusion criteria and had no exclusion criteria were included in the study. Inclusion criteria are: men and women aged 45 to 65 years old; stage II HD; COVID-19 over the last 6 months; and written informed consent of a patient to participate in the study. Exclusion criteria are: age< 45 or >65 years old, stage I and III HD, pregnancy, lactation, presence of accompanying decompensated diseases or acute conditions that, in the opinion of the researcher, can affect the results of the study; alcohol and drug addiction; presence of infectious diseases, syphilis, hepatitis B or C, HIV infection; participation in any other study; patient's refusal to sign written informed consent.

Groups of patients

A total of 109 patients with stage II HD who had undergone COVID-19 participated in the 2nd stage of the study and were randomly distributed into 2 groups:

- Group 1 (54 individuals) – patients with stage II HD who had undergone COVID-19 and who were taking combined AHPT (including statins) during the whole period of observation;

- Group 2 (55 individuals) – patients with stage II HD who had undergone COVID-19 and who during the whole period of observation were taking combined AHPT (including statins) + L-arginine complex (500 mg tablets once a day, for 12 weeks according to the 2 weeks-on/1 week-off regimen) + dihydroquercetin (25 mg tablets twice a day, for 12 weeks according to the 4 weeks-on/1 week-off regimen).

In week 0, baseline values of the following parameters were established:

1. Office SAP and DAP levels were measured by the indirect auscultatory method using an Accoson Green Light 300 sphygmomanometer (UK) according to the method by N.S. Korotkov in a sitting position (after five minutes of rest); the measurement was performed three times with an interval of 2-3 minutes; the average value of three measurements was recorded;

2. Daily AP monitoring (DAPM) parameters were determined using a daily AP monitor ABPM-04, Meditech (Hungary). The following indices of DAPM were analyzed: mean systolic (SAP m.), mean diastolic (DAP m.) AP during the day; the degree of night decrease (DND) in AP, which is defined as the difference between the level of AP (SAP and DAP respectively) during the day and night; the integral indices – hypertensive time index (HTI, %) and area index (AI) were also evaluated. Groups 1.1 and 2.1 (30 patients in each group) were formed from the patients of groups 1 and 2 to perform DAPM;

3. Endothelial regulation of vascular tone (ERVT) in groups 1.1 and 2.1 was assessed on the shoulder artery using a phased array ultrasound system equipped with a 10-MH linear transducer (Toshiba Aplio-400, Japan) according to the method proposed by D. Celermajer et al. (1992). in modification developed at V.K. Gusak Institute of Emergency and Reconstructive Surgery (Innovation proposal, certificate № 103 of September 30, 1999). The technique provides for a control group consisting of healthy volunteers (n=30);

4. To assess LM, the indices of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-CS), high-density lipoprotein cholesterol (HDL-CS), and triglycerides (TG) were analyzed.

According to the recommendations of the new Systematic Coronary Risk Evaluation 2 (SCORE2) scale, which allows determining the total risk of atherogenic cardiovascular disease, instead of a level of TCS, the level of low-density lipoprotein cholesterol (non-LHD-CS) is used – a calculated indicator determined by the formula 1:

$$\text{Non-LHD-CS} = \text{TCS} - \text{LHD-CS} \quad (1)$$

Non-LHD-CS, the value of which should be <3.7 mmol/L, is a more accurate parameter that takes into account all atherogenic particles and is superior in its ability to predict major cardiovascular complications (Ezhov et. al. 2017). The updated version of the previous SCORE scale also has an expanded age range from 40 to 90 years, including the use of the SCORE2 Older Persons scale for people aged 70 years and older. The new clinical guidelines "Lipid Metabolism Disorders" were developed by the Russian Society of Cardiology with the participation of the National Society for the Study of Atherosclerosis, approved by the Russian Ministry of Health in February 2023, and took effect on January 1, 2024.

Statistical analysis

Office SAP and DAP valued at weeks 0, 2, 4, 8, and 12; DAPM values, ERVT and LM at weeks 0 and 12.

Quantitative data obtained during the 1st stage of the study is presented in M (SD) format, where M is arithmetic mean and SD – standard deviation, as well as in the format of absolute numbers (Lyakh et al. 2006).

The results obtained in the 2nd stage of the study were processed using a specialized package of statistical programs Medical Statistics (Lyakh et al. 2006). Regression models were built and analyzed in MedCalc v.13.3.0.0 (MedCalc SoftWare bvba, 1993-2014).

Results and Discussion

A total of 1118 respondents aged 45 to 72 years participated in the questionnaire survey; the mean age was 58.6 (4.2) years. There were 537 (48.0%) males and 581 (52.0%) females.

The results obtained from the questionnaire survey indicate that patients suffering from AH for quite a long time (7-10 years) go to the pharmacy to purchase AHODs. AHPT taken by patients are ineffective, as evidenced by the levels of SAP and DAP, which significantly exceed the recommended AP (<140/90 mmHg). Their mean values are 148.9 (4.6) mmHg and 85.5 (1.6) mmHg in men and 149.5 (4.3) mmHg and 83.3 (2.5) mmHg in women (SAP and DAP, respectively).

According to the data obtained from the questionnaires, 248 (46.2%) men and 262 (45.1%) women underwent COVID-19; most of them three to six months earlier. Of the HD patients who underwent COVID-19, the majority (92-95%) reported worsening AP control:

234 men and 241 women. Only 16 men and 21 women (6.5-8.7%) consulted a physician due to inadequate AP control.

It is important to note that quite a large number of respondents, namely 187 (34.8%) men and 214 (36.8%) women, expressed potential willingness to participate in the AHPT improvement program.

The analysis of AHPT conducted in respondents showed that its "leader" is enalapril, which is taken by 30.6% of respondents. The other positions in the top-5 were distributed as follows: lisinopril – 16.2%; bisoprolol – 15.1%; amlodipine – 14.4%; and captopril – 7.6%. Next come furosemide – 3.6%, losartan – 3.4%, metoprolol – 2.5%, valsartan – 1.3%, nebivolol – 1.2%, nifedipine – 1.1%, torasemide – 0.7%, candesartan – 0.9%, perindopril – 0.6%, atenolol – 0.5%, indapamide – 0.3% and others.

The data presented in Figure 1 indicate that patients receive predominantly monotherapy, and 3.4% of HD patients do not take AHODs regularly.

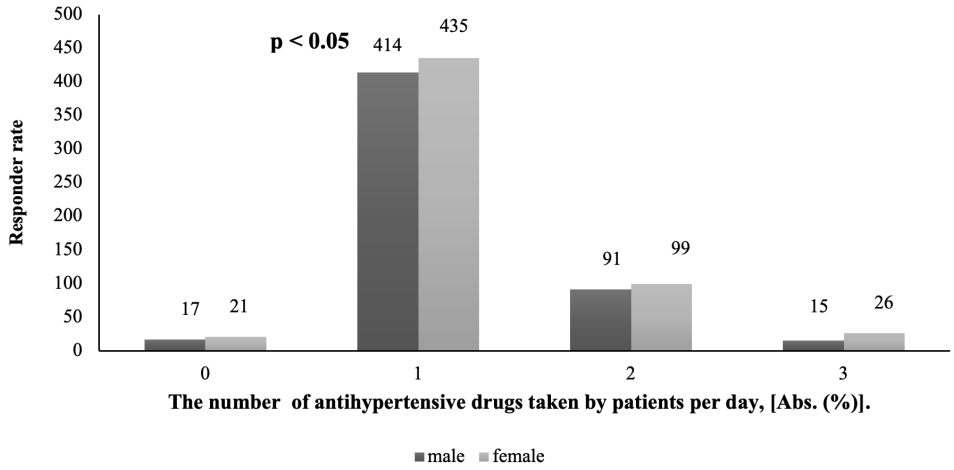


Figure 1. The number of antihypertensive drugs taken by patients per day, [Abs. (%)].

The data presented in Tables 1 and 2 show that inclusion of L-arginine + dihydroquercetin complex in combined AHPT (including statins) of patients with stage II HD who underwent COVID-19 (Group 2) provided normotonic values of SAP and DAP (<140/90 mm Hg), which were achieved by the end of the 2nd week of treatment. In Group 1 patients who had received only combined AHPT (including statins), similar changes in AP levels were achieved only by the end of the 4th week.

Table 1. Dynamics of office SAD (mm Hg) in patients with stage II HD during different variants of AHPT

Patient group	Statistical indicator	Treatment period (weeks)				
		0	2	4	8	12
Group 2 (n=54)	M	147.6	141.5	136.6*	135.3*	135.5*
	Me	149.4	143.1*	135.1*	137.1*	136.6*
	25 %	151.4	139.1*	132.3*	139.1*	138.6*
	75 %	149.8	144.3*	138.5*	133.2*	134.4*
	m	11.2	8.5	7.1	6.6	6.5
Group 2(n=55)	M	148.4	134.7*	127.8*#	127.7*#	125.7*#
	Me	151.1	137.2*	126.6*#	126.9*#	124.6*#
	25 %	154.1	136.9*	129.1*#	129.1*#	126.8*#
	75 %	146.7	133.8*	123.7*#	124.5*#	124.1*#
	m	10.3	8.3	7.3	6.4	6.4

Note: M – mean value; Me – median; 25% – lower quartile; 75% – upper quartile; m – median error; * – p<0.05 compared to the pre-treatment index; # – denotes indicators for which statistically significant (p<0.05) difference from the indicators of the 1st and 2nd groups were revealed.

Table 2. Dynamics of office DAP (mm Hg) of patients with stage II HD during different variants of AHPT

Patient group	Statistical indicator	Treatment period (weeks)				
		0	2	4	8	12
Group 1(n=54)	M	97.1	92.3	87.8*	80.9*	75.3*
	Me	95.1	91.7	88.1*	81.3*	77.2*
	25 %	98.3	94.7	85.8*	84.6*	79.1*
	75 %	94.1	89.1	89.2*	79.1*	74.0*
	m	5.3	5.2	5.3	4.5	4.4
Group 2(n=55)	M	96.7	87.1*	73.0*#	71.2*#	68.3*#
	Me	95.4	85.6*#	75.2*#	74.0*#	69.5*#
	25 %	93.7	84.1*#	76.7*#	73.1*#	69.7*#
	75 %	97.9	88.7*#	72.1*#	70.6*#	64.2*#
	m	5.2	5.1	4.5	4.2	4.1

Note: M – mean value; Me – median; 25% – lower quartile; 75% – upper quartile; m – median error; * – $p<0.05$ compared to the pre-treatment index; # – denotes indicators for which statistically significant ($p<0.05$) difference from the indicators of the 1st and 2nd groups were revealed.

As we can see from Tables 1 and 2, only combined AHPT + L-arginine + dihydroquercetin complex, starting from the 4th week of treatment, provided reduction of office SAP <130 mm Hg and office DAP <80 mm Hg. Levels of SAP and DAP exceeding these values (>130/80 mm Hg) are now a criterion for the presence of AH, according to existing international recommendations. Thus, the inclusion of L-arginine + dihydroquercetin complex in the composition of combined AHPT in patients with stage II HD who underwent COVID-19 increases the efficacy of treatment and provides AP control within normotonic values during 12 weeks of treatment.

Analyzing the results of DAPM, it was found that in the course of treatment the indices of SAP m. and DAP m., baseline, area index, hypertensive time index (HTI) (both SAP and DAP) decreased ($p<0.05$) in both groups of patients by the 12th week (Table 3). In contrast, DND indices (for both SAP and DAP) increased accordingly ($p<0.05$). The nightly decrease was more significant in Group 2.1 patients (Table 3), who had received L-arginine + dihydroquercetin as part of AHPT. The DND values (%) for SAP and DAP in Group 2.1 patients were 17.6% and 18.0%, respectively, which was statistically significantly higher ($p<0.05$) than in Group 1.1.

At the same time, it should be noted that the patients of both groups achieved a normal index of DND value, which is 10-20% of nightly AP reduction from the daytime AP level (Table 3).

Thus, it can be stated that patients of both groups due to treatment moved to the "Dipper" category – with a physiologic AP decrease at night. This fact indicates that the use of combined AHPT (Group 1.1) and inclusion of L-arginine + dihydroquercetin (Group 2.1) was effective.

If we compare the mean values of DAPM parameters, namely HTI, baseline (both for SAP and DAP) of Group 1.1 patients after 12 weeks of treatment with those of Group 1.2 patients, it should be noted that these results in Group 1.2 are statistically significantly ($p<0.05$) better (Table 3).

The analysis of HTI indices (%) indicates (Table 3) that in patients of both groups before the beginning of treatment there was a rather high proportion of daytime AP measurements exceeding the norm, which indicates the organism to be overloaded by pressure. "Critical" values of daytime AP were considered to be 140/90 mm Hg and night-time AP – 120/80 mm Hg. In patients of both groups, this index was "elevated", i.e. the percentage of daytime AP measurements was >30%, when AP above the norm was registered.

In the course of treatment, there was a decrease ($p<0.05$) in HTI indices in all patients (Table 3). This decrease ($p<0.05$) was most significant in Group 1.2, namely for SAP – in 2.4 times and for DAP – in 2.2 times and reached the values of 29.6% for SAP and 28.2% for DAP. At the same time, it should be noted that patients in none of the groups reached the " borderline" level of HTI – 10-25%. According to the recommendations of the American Society of Hypertension (American Society of Hypertension, 2020), a normal value of HTI is less than 15%, while exceeding HTI more than by 30% indicates undoubtedly elevated AP. In Group 1.1 patients, this index remained "elevated" (>30%) despite its significant reduction.

Table 3. Dynamics of DAPM indicators in patients with stage II HD during different variants of AHPT

Treatment period, weeks	Statistical indicator	Group 1.1 (n=30)	Group 2.1(n=30)
Daily SAP m., mm Hg.			
0 week	M	144.7	145.2
	Me	144.1	144.2
	25 %	141.1	143.9
	75 %	146.2	146.9
	m	3.2	3.3
12 week	M	133.2$	121.5$*
	Me	132.4$	120.7$*
	25 %	130.4$	119.5$*
	75 %	134.5$	121.9$*
	m	2.8	2.2
Daily DAP m., mm Hg.			
0 week	M	94.7	94.5
	Me	95.2	95.3
	25 %	93.6	93.4
	75 %	96.5	96.7
	m	1.4	1.3
12 week	M	83.6$	71.0*$
	Me	84.3$	74.1*$
	25 %	82.5$	72.3*$
	75 %	85.2$	74.9*$
	m	1.2	1.4
DND SAP (%)			
0 week	M	7.6	7.7
	Me	7.7	7.5
	25 %	7.4	7.1
	75 %	7.9	7.9
	m	0.3	0.4
12 week	M	11.7$	17.6$*#
	Me	11.9$	17.3$*#
	25 %	11.5$	16.8$*#
	75 %	12.1$	17.9$*#
	m	0,3	0.4
DND DAP (%)			
0 week	M	7.9	7.6
	Me	7.7	7.4
	25 %	7.4	7.3
	75 %	7.6	7.7
	m	0.2	0.3
12 week	M	12.0$	18.0$*
	Me	11.7$	17.6$*
	25 %	11.4$	17.5$*
	75 %	12.3$	18.3$*
	m	0.2	0.2
baseline SAP			
0 week	M	374.8	373.7
	Me	376.4	374.3
	25 %	368.4	364.8
	75 %	381.6	378.1
	m	12.3	13.1
12 week	M	304.4$	247.7$*
	Me	310.6$	248.7$*
	25 %	301.7$	232.4$*
	75 %	320.1$	253.4$*
	m	9.4	10.3

Table 3. Dynamics of DAPM indicators in patients with stage II HD during different variants of AHPT (ending)

Treatment period, weeks	Statistical indicator	Group 1.1 (n=30)	Group 2.1(n=30)
baseline DAP			
0 week	M	194.7	197.7
	Me	193.3	201.4
	25 %	186.5	193.4
	75 %	192.5	206.1
	m	7.3	7.2
12 week	M	133.5$	79.4$*
	Me	134.2$	78.5$*
	25 %	128.1$	74.2$*
	75 %	135.2$	81.3$*
	m	7.1	4.9
HTI SAP (%)			
0 week	M	71.5	70.0
	Me	72.3	69.8
	25 %	69.8	67.4
	75 %	71.9	71.3
	m	3.3	3.1
12 week	M	59.0$	29.6$*
	Me	58.9$	30.2$*
	25 %	56.5$	29.3$*
	75 %	60.7$	31.2$*
	m	3.4	1.2
HTI DAP (%)			
0 week	M	62.9	63.3
	Me	61.4	64.1
	25 %	59.3	62.1
	75 %	64.2	65.9
	m	2.7	2.2
12 week	M	55.4$	28.2$*
	Me	56.1$	28.6$*
	25 %	54.6$	26.4$*
	75 %	56.9$	30.1$*
	m	2.2	2.3

Note: M – mean value; Me – median; 25% – lower quartile; 75% – upper quartile; m – median error; * – denotes indicators for which statistically significant ($p<0.05$) difference from Group 1.1 in the corresponding period was revealed; $ – indicators for which statistically significant ($p<0.05$) difference of the indicator from the initial one was revealed.

The smallest decrease in HTI, namely by 16.9% for SAP and by 11.1% for DAP by the end of the 12th week was observed in Group 1.1 of patients, who had received only combined AHPT. This indicates that the addition of L-arginine + dihydroquercetin to combined AHPT contributes to a more significant increase in the efficacy of AHPT.

The effectiveness of AHPT can also be judged by the initial indicator, which demonstrates what hypertensive load is acting on the organism (i.e., for how long elevated AP is observed and how on average it exceeds the upper limit of the range). The analysis shows that the best results for the majority of indicators were obtained for patients in Group 1.2 (Table 3). The same is confirmed by the analysis of baseline indicators (for SAP and DAP): the reduction of SAP baseline indicator from the baseline indicator for 12 weeks in Group 2.1 was 1.5 times and for DAP – 2.5 times.

Thus, it was found that in patients with stage II HD, who underwent COVID-19, statistically significant ($p<0.05$) improvement of the results of most indicators of the daily AP profile (SAP m. and DAP m. per day; DND for SAP and DAP) is provided by combined AHPT, as well as by the inclusion of L-arginine + dihydroquercetin. Inclusion of L-arginine + dihydroquercetin in combined AHPT provided also the most significant improvement of such integral indices as HTI and baseline, which confirms the importance of using this combination for treatment of HD patients (possibly for longer periods of time).

Table 4. Dynamics of brachial artery diameter parameters (cm) in response to blood flow acceleration in patients with stage II HD and in the control group under different variants of AHPT

Treatment period, weeks	Statistical indicator	Group 1.1 (n=30)	Group 2.1 (n=30)	Control (n=30)
Before occlusion				
0 week	M	0.542	0.543	0.553
	Me	0.541	0.545	0.554
	25 %	0.539	0.539	0.552
	75 %	0.545	0.548	0.556
	m	0.002	0.002	0.002
12 week	M	0.542	0.542	0.552
	Me	0.541	0.539	0.549
	25 %	0.537	0.537	0.539
	75 %	0.546	0.548	0.551
	m	0.003	0.003	0.003
After occlusion				
0 week	M	0.578	0.582	0.661*
	Me	0.580	0.581	0.663*
	25 %	0.576	0.578	0.659*
	75 %	0.584	0.584	0.667*
	m	0.003	0.003	0.003
12 week	M	0.592*	0.662*$	0.663*
	Me	0.590*	0.663*$	0.664*
	25 %	0.587*	0.660*$	0.662*
	75 %	0.594*	0.665*$	0.667*
	m	0.003	0.003	0.003

Note: M – mean value; Me – median; 25% – lower quartile; 75% – upper quartile; m – median error; * – parameters for which statistically significant ($p<0.05$) difference from the parameters before occlusion was revealed; $ – parameters for which statistically significant ($p<0.05$) difference from the parameters of Group 1.1 was revealed.

After treatment (after 12 weeks), no statistically significant differences were found in the mean values of brachial artery diameter before occlusion in both groups ($p=0.53$, Kruskall-Wallis test), and they did not differ from the values before treatment ($p=0.76$, Kruskall-Wallis test). After occlusion, the mean values of brachial artery diameter differed ($p<0.05$). So, in Group 2.1 the analyzed index was higher than in Group 1.1, and also reached the index in the control group, which indicates higher efficiency of combined AHPT + complex L-arginine + dihydroquercetin in restoration of vasodilating function of vascular endothelium (Table 4).

Thus, it has been established that in Group 2.1 of stage II HD patients, overcoming endothelial dysfunction is observed after 12 weeks of complex treatment including standard AHPT + L-arginine + dihydroquercetin. The change of brachial artery diameter in response to acceleration of blood flow velocity after external occlusion in this group of patients after 12 weeks of treatment is similar to the diameter change in healthy volunteers.

The results shown in Table 5 indicate that in both groups of patients with moderately severe COVID-19 stage II HD patients, the baseline non-high-density lipoprotein cholesterol (non-HDL-CS) index is 1.2 times higher than the target level (<3.7 mmol/L). In patients of both groups, the values of LM indices indicate dyslipidemia, namely: TCS > 4.9 mmol/L; CS > 1.7 mmol/L; and CS-LPLS > 3.0 mmol/L.

All patients included in the study received statins mainly in minimal doses. This can probably explain the insufficient efficacy of hypolipidemic therapy. As it was already mentioned, within the framework of the 1st stage (week 0), correction of the drug regimen was carried out (if necessary). Correction of statin regimen was also performed.

Table 5. Dynamics of LM indices in stage II HD patients who underwent COVID-19

Treatment period		Group 1 (n=54)	Group 2 (n=55)
TCS (mmol/L)			
0 week	M	5.36	5.39
	Me	5.35	5.40
	25 %	5.33	5.36
	75 %	5.39	5.42
	m	0.37	0.38
12 week	M	4.88*	4.31#$
	Me	4.87	4.32
	25 %	4.84	4.27
	75 %	4.52	4.35
	m	0.32	0.26
TG (mmol/L)			
0 week	M	1.94	1.97
	Me	1.93	1.98
	25 %	1.92	1.95
	75 %	1.96	1.99
	m	0,12	0,14
12 week	M	1.70	1.64*$
	Me	1.71	1.61
	25 %	1.68	1.60
	75 %	1.72	1.66
	m	0,11	0,11
LHD-CS (mmol/L)			
0 week	M	0.98	0.97
	Me	0.97	0.98
	25 %	0.96	0.95
	75 %	1.00	0.99
	m	0,06	0,06
12 week	M	1.07	1.18*$
	Me	1.08	1.17
	25 %	1.05	1.16
	75 %	1.09	1.20
	m	0,07	0,08
LPLS-CS (mmol/L)			
0 week	M	3.02	3.08
	Me	3.03	3.07
	25 %	3.00	3.06
	75 %	3.04	3.10
	m	0,18	0,19
12 week	M	2.41*	1.51#$
	Me	2.39	1.53
	25 %	2.36	1.50
	75 %	2.45	1.57
	m	0,14	0,15
Non-LHD-CS (mmol/L)			
0 week	M	4.48	4.42
	Me	4.47	4.43
	25 %	4.45	4.40
	75 %	4.50	4.45
	m	0,24	0,25
12 week	M	3.81*	3.13#$
	Me	3.80	3.15
	25 %	3.78	3.10
	75 %	3.85	3.17
	m	0.23	0.19

Note: * – indicators for which a statistically significant ($p<0.05$) difference from baseline was found; # – indicators for which a statistically significant ($p<0.001$) difference from baseline was found; $ –indicators for which a statistically significant ($p<0.05$) difference from the indicators of Group 1 was revealed.

During the study, positive dynamics of LM indices was observed in patients of both groups (Table 5). Thus, in Group 1 patients, positive dynamics of TCS and high-density lipoprotein cholesterol (LPLS-CS) was statistically significant ($p<0.05$). The target values for TCS (<4.9 mmol/L) and LHD-CS (<3.0 mmol/L) were also reached (Table 5).

At the same time, the target value of TG indicator (<1.7 mmol/L) was not achieved. The target value for the calculated index of non-LHD-CS (<3.7 mmol/L) was also not achieved (Table 5). In this regard, Group 1 patients were prescribed inclusion of ezetimibe in the hypolipidemic therapy, which is recommended if the LPLS-CS index during treatment did not decrease by 50% of the initial value or its level is >1.4 mmol/L.

More significant changes in LM were revealed in Group 2 patients, who took L-arginine + dihydroquercetin complex as part of combined AHT in doses established by the study design. Thus, in patients of Group 2, there was a significant (by 20-30%) decrease in TCS and TG indices. The decrease of the calculated index of non-LHD-CS (by 30%) was also pronounced (Table 5).

In spite of the fact that in Group 2 patients, the LPLS-CS index did not reach the target value <1.4 mmol/L during treatment, its reduction was >50%; that is why ezetimibe was not recommended for these patients.

Conclusion

1. Insufficient efficacy of AHPT taken by the HD patients living in Donetsk to a significant extent is a consequence of COVID-19 leading to vascular endothelial dysfunction, and incorrect treatment (mainly monotherapy). In order to overcome this situation, it is necessary to search for additional pharmacotherapeutic possibilities of endothelial dysfunction correction in this cohort of patients.

2. Inclusion of L-arginine complex (500 mg tablets once a day, for 12 weeks according to the 2-weeks-on/1-week-off regimen) + dihydroquercetin (25 mg tablets twice a day, for 12 weeks according to the 4-weeks-on/1-week-off regimen) as a part of combined AHPT (including statins) in patients with stage II HD, who underwent COVID-19, increased its efficacy, which was manifested by achievement of normotonic values of office SAP and DAP (<140/90 mm Hg) by the end of the 2nd week of treatment compared to combined AHPT (including statins) in comparison with combined AHPT (by the end of the 4th week of treatment). Reduction of office SAP (<130 mm Hg) and DAP (<80 mm Hg) was achieved starting from the 4th week of treatment only when L-arginine + dihydroquercetin was included in combined AHPT complex.

Inclusion of L-arginine + dihydroquercetin complex in the combined AHPT of stage II HD patients who underwent COVID-19 for 12 weeks was more effective than combined AHPT in providing improvement of DAPM parameters, which was manifested by:

- <30% decrease in HTI of SAP and HTI of DAP;
- 33.1% reduction of SAP and 40.3% reduction of DAP from baseline.

3. Inclusion of L-arginine + dihydroquercetin in the composition of combined AHPT of patients with stage II HD who underwent COVID-19 for 12 weeks promoted the elimination of vascular endothelial dysfunction, which was manifested by the change in the brachial artery diameter in this group in response to acceleration of blood flow velocity after external occlusion similar to the change in the brachial artery diameter in the group of healthy volunteers.

4. Inclusion of L-arginine + dihydroquercetin complex in the composition of combined AHPT in patients with stage II HD, who underwent COVID-19, more effectively than combined AHPT (including statins) affects LM, which is manifested by improvement of its key parameters (TCS, TG, LPLS-CS and HDL-CS), as well as the calculated index of non-HDL-CS.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statement

This research was approved by the meeting of the Ethical Committee of M. Gorky Donetsk State Medical University, Minutes No. 69/5-1 of November 24, 2021.

Data availability

All of the data that support the findings of this study are available in the main text.

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