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Research Article

Relationship of the main indicators of systemic COVID-associated endotheliopathy with the morphofunctional state and hemodynamics of the retina and chorioid in the acute period of the disease

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BACKGROUND: Nonspecific angio- and retinopathy is one of the clinical manifestations of a new coronavirus infection. The frequency of occurrence of these changes in people with severe COVID-19 does not exceed 55%. The causes, course and consequences of these microcirculatory disorders of the retina are currently not well understood.

AIM: To study and compare of retinal morphometric parameters and systemic endothelial dysfunction markers, as well as the main clinical and laboratory parameters in patients with moderate and severe coronavirus infection during convalescence.

MATERIALS AND METHODS: The study involved 44 patients (86 eyes) who had COVID-19 during the previous 3 months, who were divided into 2 groups: with moderate and severe disease. The control group consisted of 18 healthy volunteers (36 eyes). All patients underwent a standard ophthalmological examination and optical coherence tomography, which included an assessment of the choroidal thickness (CT) and measurement of the mean diameter of the peripapillary arteries (MAD) and veins (MVD). During hospitalization, all patients underwent a laboratory study of venous blood parameters, as well as an assessment of the microcirculation of the sublingual plexus by examining the density of the endothelial glycocalyx (PBR) using the GlycoCheck.

RESULTS: In patients who underwent COVID-19, there was a significant increase in CT relative to the control group, amounting to 308, 344 and 392 μm, respectively. The most pronounced difference was observed between MVD in patients with severe infection and the control group (119.1 μm vs. 99.2 μm). In patients with moderate and severe COVID-19, MAD and MVD were positively correlated with TC, with $r = 0.389$ and $r = 0.584$, respectively. MVD also correlated with the level of leukocytes ($r = 0.504$), the ESR value ($r = 0.656$). Correlations between MVD and data characterizing the state of the glycocalyx in the sublingual vascular plexus were revealed: the filling of small capillaries with erythrocytes ($r = -0.587$), as well as the marginal perfusion value in large capillaries 20–25 μm ($r = 0.479$) and PBR ($r = 0.479$). Only significant differences and correlations are shown ($p < 0.005$).

CONCLUSIONS: In patients who underwent moderate and severe COVID-19 during the convalescence period (up to 30 days), an increase in the diameter of peripapillary vessels and TC is observed, proportional to the severity of COVID-19, laboratory markers of systemic inflammation and hypercoagulation (the number of leukocytes, the ESR value, D-dimer and prothrombin), which indicates the inflammatory nature of the changes. The severity of postcovid retinal microangiopathy correlates with indicators detecting a decreasing of the endothelial glycocalyx thickness in the sublingual capillary plexus, which indirectly indicates a connection with systemic endotheliopathy.

Keywords: COVID-19; coronavirus infection; optical coherence tomography; peripapillary artery diameter; peripapillary vein diameter; choroidal thickness; endothelial glycocalyx; endothelial dysfunction.

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Научная статья

Взаимосвязь основных показателей системной COVID-ассоциированной эндотелиопатии с морфофункциональным состоянием и гемодинамикой сетчатки и хориоидеи в острый период заболевания

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Актуальность. Неспецифическая ангио- и ретинопатия является одним из клинических проявлений новой коронавирусной инфекции. Частота встречаемости данных изменений у лиц с тяжёлым течением COVID-19 не превышает 55 %. Причины, течение и последствия этих микроциркуляторных расстройств сетчатки в настоящее время изучены недостаточно.

Цель — изучение и сопоставление морфометрических показателей сетчатки и маркеров системной эндотелиальной дисфункции, а также основных клинико-лабораторных показателей у пациентов со средней и тяжёлой формой коронавирусной инфекции в период реконвалесценции.

Материалы и методы. В исследование вошло 44 пациента (86 глаза), перенёсших COVID-19 в течение предшествующих 3 мес., которые были разделены на 2 группы: со среднем и тяжёлым течением заболевания. Контрольную группу составили 18 здоровых добровольцев (36 глаз). Всем пациентам проводилось стандартное офтальмологическое обследование и оптическая когерентная томография с оценкой толщины хориоидеи (ТХ) и измерением среднего диаметра перипапиллярных артерий (СДА) и вен (СДВ). В период госпитализации выполнено лабораторное исследование показателей венозной крови, а также оценка микроциркуляции сублингвального сплетения путём исследования плотности эндотелиального гликокаликса (PBR) аппаратом GlycoCheck.

Результаты. У пациентов, перенёсших COVID-19, отмечалось значимое, относительно группы контроля, увеличение ТХ, составляющее 308, 344 и 392 мкм соответственно. Наиболее выраженная разница наблюдалась между показателем СДВ у пациентов с тяжёлым течением инфекции и группой контроля (119,1 мкм против 99,2 мкм). У пациентов с среднем и тяжёлым течением COVID-19 показатели СДА и СДВ положительно коррелировали с ТХ, при $r = 0,389$ и $r = 0,584$ соответственно. СДВ также коррелировал с уровнем лейкоцитов ($r = 0,504$), величиной СОЭ ($r = 0,656$). Выявлены корреляции СДВ и данными, характеризующими состояние гликокаликса в сублингвальном сосудистом сплетении: заполнением мелких капилляров эритроцитами ($r = -0,587$), а также величиной пограничной перфузии в крупных капиллярах 20-25 мкм ($r = 0,479$) и PBR ($r = 0,479$). Приведены только значимые различия и корреляции ($p < 0,005$).

Выводы. У пациентов, перенёсших COVID-19 в средней и тяжёлой форме в период реконвалесценции (до 30 сут), наблюдается увеличение диаметра перипапиллярных сосудов и ТХ, пропорциональное степени тяжести COVID-19, лабораторным маркерам системного воспаления и гиперкоагуляции (количеством лейкоцитов, величиной СОЭ, D-димера и протромбина), что свидетельствует о воспалительной природе изменений. Степень выраженности постковидной микроангиопатии сетчатки коррелирует с показателями, свидетельствующими об уменьшении толщины эндотелиального гликокаликса в сублингвальном капиллярном сплетении, что косвенно свидетельствует о связи с системной эндотелиопатией.

Ключевые слова: COVID-19; коронавирусная инфекция; оптическая когерентная томография; диаметр перипапиллярных артерий; диаметр перипапиллярных вен; толщина хориоидеи; эндотелиальный гликокаликс; эндотелиальная дисфункция.

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BACKGROUND

The new coronavirus infection (COVID-19) still represents a serious medical and social problem. Nowadays, the humanity faces already the seventh wave of the disease and, taking into consideration the coronavirus ability to mutate rapidly, an assumption is made that it will fall into line with already known seasonal viral diseases [1]. New SARS-CoV-2 strains, such as Omicron, Centaurus, and Deltacron, possess higher contagiousness, more rarely lead to bad after-effects, but in the same manner as for predecessors, their major target becomes the endothelium, the lesion of which leads to impaired microcirculation in organs, to development of a syndrome similar to the disseminated intravascular coagulation (DIC) syndrome, causing to multiple organ failure and death. Today, active search of methods to evaluate endothelial injury is under way. Existing methods are aimed to reveal endothelial dysfunction: detection of desquamated endotheliocytes, glycocalyx status estimation [2], testings of von Willebrand factor and of other recognized endothelial dysfunction markers.

Microcirculation investigations are traditionally carried out on most accessible parts of the body — nail fold and mucosa of the sublingual area. One more object for microcirculation investigation is the retina. Retinal vessels could be well visualized, are accessible for photoregistration. Using fluorescein angiography and optical coherence tomography angiography methods, it is easy to in vivo evaluate dimensions, patency of retinal vessels, to estimate perfusion and permeability of the vascular wall, as well as to measure the vessel density in the capillary plexus. Whereas the retina is the most metabolically-active tissue in the human organism — it is an indispensable marker for microcirculation evaluation in such diseases as diabetes mellitus, arterial hypertension, etc. [3]. At present, there are multiple confirmations on the presence of a COVID-associated angio- and retinopathy as well [4–6].

Under the term “COVID-associated retinopathy” the whole of angio- and retinopathy manifestations in patients during the acute and sub-acute period of coronavirus infection is implied, including significant dilatation and tortuosity of peripapillary vessels, appearance of cotton-wool spots and of intraretinal hemorrhages. The prevalence of COVID-associated retinopathy is poorly known, but according to various data, during first 60 days from the disease onset, its probability may be 55% [7]. Most prominent manifestations of angio- and retinopathy are registered at the disease severe course immediately during its acute period and during following 30 days. At present time, the most large prospective cross-sectional controlled study, estimating the prevalence and clinical manifestations of the COVID-associated retinopathy, is SERPICO-19 [8].

The confirmation of this clinical study was established as a result of histological, immuno-histochemical, molecular-biological, and electron-microscopical analysis of the retina of patients who died of coronavirus infection. In the autopsy material, viral fragments, perivascular gliosis, and retinal capillary occlusion were found, in some cases, there was a cellular infiltration of the vitreous. Of particular interest is the fact, that even in patients after mild and in some cases even asymptomatic infection course, during the acute and sub-acute period, there were signs of retinal capillary perfusion impairment [10, 11]. The most probable cause of it could be a systemic endotheliitis [12], caused by direct viral action [13], secondary injury of the endotheluim as a result of autoimmune answer [14], as well as hemostasis disturbance, associated with coronavirus infection [15, 16].

Any pathological action on the vascular endothelium leads to the impairment of its function, first of all vascular tone regulation, maintenance of a balance between fibrinolysis and hypercoagulation, provision of thromboresistance. Endothelial disfunction may be a local, as well as systemic process [17], at that it may not have any clinical manifestations, or may lead to acute occlusion of pulmonary, renal capillaries as well of those of different organs [13, 15]. Preclinical detection of endothelial dysfunction markers in coronavirus infection is a very important objective, which allows to maximally increase for patients the quality level of treatment and to decrease the risk of possible complications. At present, there are no large-scale studies estimating the relation between the systemic COVID-associated endotheliopathy and the COVID-associated angioretinopathy.

MATERIALS AND METHODS

During the period from April 2021 till April 2022, at the premises of the Chair and Clinic of ophthalmology named after Professor Y.S. Astakhov of the Academician I.P. Pavlov First St. Petersburg State Medical University of, 44 patients (86 eyes) were examined after moderate severity and severe COVID-19 infection. The median age was 57 years (from 23 to 82 years), from 44 patients, 26 were women. Investigated patients were divided into 2 groups, according to the severity of the disease: 1st group included 24 patients after moderate severity COVID-19, and the 2nd group — 18 patients with severe form of the disease. The control group consisted out of 18 volunteers, who did not catch the coronavirus infection and were not vaccinated during 6 months preceding the study (the median age was 43 years, there were 9 women).

As main inclusion criterion served the history of COVID-19 infection (confirmed by the polymerase chain reaction of the swab from the oropharynx) of no more

Table 1. Characteristics of patients from study and control groups

Таблица 1. Общая характеристика пациентов из групп исследования и контрольной группы

Index	Control group	1st group	2nd group	*p*
Patients (eyes)	18 (36)	18 (36)	24 (46)	.082
Males, *n*	9 (50 %)	8 (44 %)	12 (50 %)	.234
Age, years, *Me* [min; max]	43 [21; 58]	56 [23; 82]	62 [32; 75]	.052
BCVA, *Me* [min; max]	0.96 [0.8; 1.0]	0.94 [0.7; 1.2]	0.96 [0.6; 1.2]	.634
IOP, *Me* [min; max]	16.5 [10; 19]	14.5 [10; 20]	16.5 [13; 20]	.494
SE, *Me* [min; max]	–1.25 [–5.25; +1.5]	–0.5 [–4.5; +3.0]	–0.75 [–5.0; +3.5]	.437

Note. Significance levels are shown for the Kruskal–Wallis rank coefficient and the chi-square in binom distribution. BCVA — best corrected visual acuity in high contrast; IOP — intraocular pressure; SE — spherical equivalent of the patient's refraction.

than 3 months from the first symptoms. At the time of research conduct, practically all patients received treatment at the premises of the pulmonology department of the hospital therapy clinic of the I.P. Pavlov FSPbSMU.

Exclusion criteria: age less than 18 years, non-compensated systemic diseases, pregnancy, history of ophthalmic surgery or of some ocular disease. Aiming at more confident interpretation of retinal optical coherence tomography (OCT) data, patients with refractive errors of more than 5 diopters from emmetropia and with astigmatism of more than 2 diopters.

All study participants were subjects to standard ophthalmologic examination including visual acuity testing using the TCP-2000 screen (Topcon, Japan) with high (100%) contrast, tonometry (iCare tonometer, USA), autorefractometry with subjective refractometry, anterior segment biomicroscopy, and biomicroophthalmoscopy using aspheric lenses.

Groups were homogeneous according to indices of sex, age, best corrected visual acuity, intraocular pressure (Table 1).

Besides, OCT of the retinal and the optic nerve was performed with caliber measurement of the peripapillary vessels. OCT was carried out using the device Spectralis OCT+HRA (Heidelberg Engineering, Germany) with additional EDI-OCT (Enhanced Depth Image) function. The retinal thickness was measured in 9 main sectors (according to the EFDRS scheme); the neuroretinal rim thickness (according to the ONH protocol), as well as the average thickness of the retinal nerve fiber layer within the circular C-scan of 3.2 mm diameter. The calibrometry of peripapillary arteries and veins was performed manually by two operators, using the tomograph's software tools on en-face HRA-images at 200% magnification. The vessel's width was taken across its course at the point of crossing between the C-scan of 3.2 diameter (protocol of the retinal nerve fiber layer measurement) with the aim of measurement standardization in different patients (Fig. 1). The vascular lumen was measured, its boundaries being determined according to light reflex limits on the HRA-image. The diameter and the lumen of vessels were determined by two operators in four main vascular arcades; and based on all carried out measurements, with the aim of univercialization, 4 values were calculated for each eye — mean artery diameter (MAD) in μm, mean vein diameter (MVD) in μm, and the ratio of the mean lumen diameter to the diameter of the vessel.

In a similar way, subfoveolar measurements of choroidal thickness were performed (protocol of retinal examination using EDI-OCT). Choroidal thickness is taken as the distance from the Bruch's membrane to the interior scleral surface, protracted perpendicular to the retina.

In all 1st and 2nd group patients, during the hospitalization at COVID-19 acute phase, a laboratory testing of venous blood was carried out. It included a complete blood count (number of red blood cells, leucocytes, platelets, white blood cell differential, erythrocyte sedimentation rate, hematocrit), metabolic panel (glycated hemoglobin, C-reactive protein, ionogram, levels of urea, creatinine, aspartat aminotransferase, alanine aminotransferase, lactate dehydrogenase, bilirubin, lipid profile), coagulation panel (fibrinogen, activated partial thromboplastin time, prothrombin, international normalization ratio, prothrombin time, ferritin, and D-dimer). For analysis in the present study, we took only indices, obtained at the first blood sampling, before the start of the main therapy.

To provide evaluation of the microcirculatory bed, we carried out the investigation of the vascular endothelial glycocalyx (VEGLX) using the instrument GlycoCheck Measurement System Software Version 5.2 (dark-field microscopy of the capillary plexus of the sublingual mucosa with videoregistration option). The GlycoCheck system is used for visualization and characterizing of the perfused boundary region (PBR index) and capillary density (Fig. 2). The PBR index was estimated according

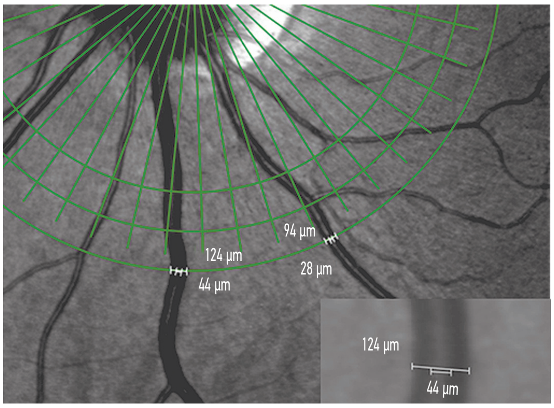

Fig. 1. Scheme for measuring the diameter of vessels and their lumens in the inferotemporal quadrant of the right eye using the built-in tomograph tools on the HRA image

Рис. 1. Схема измерения диаметра сосудов и их просветов в нижневисочном квадранте правого глаза с помощью встроенных инструментов томографа на HRA-изображении

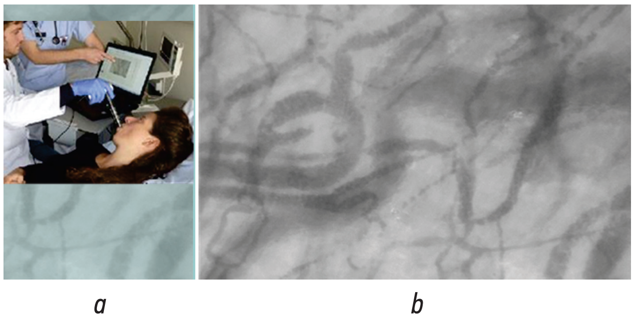

Fig. 2. Examination of the glycocalyx of mucosal capillaries in the sublingual area using the GlycoCheck system: *a* — general view of the patient; *b* — random frame from the camera of the GlycoCheck system, magnification ×325

Рис. 2. Исследование гликокаликса капилляров слизистой оболочки в сублингвальной области с помощью системы GlycoCheck: *a* — общий вид исследования пациента; *b* — кадр с камеры системы GlycoCheck, увеличение ×325

to the submersion degree of red blood cells into the glycocalyx depth in 5–25 μm with low and high blood flow velocity. The more red blood cells are buried, the more significant is the glycocalyxl damage. In contrast to the OCT-angiograph's principle of action, the capillary density value in the GlycoCheck system is calculated not on the basis of red blood cell movement in the vascular lumen, but according to the total number of 4–6 μm diameter capillaries per field of view, at least half-filled by red blood cells at point of time — the RBC filling parameter. To this particular system, the specific parameter is the design index Microvascular Health Score summing up the values of the endothelial status.

Data statistical analysis was carried out using the IBM SPSS Statistics v.23. All formed patient's groups had an uniform composition, this was confirmed using Kruskal–Wallis rank coefficient for three unconjugated samples. The significance of differences between unconjugated samples of patients with COVID-19 various severity degree and the control group was estimated pairwise using the non-parametric Mann–Whitney criterion. Correlations both between values inside the groups and between all the values were revealed using the rank Pearson's rank correlation coefficient. For descriptive statistics, the median value or that of average in combination with minimum and maximum value identification within the group limits.

RESULTS

Under all measured morphometric indices, between groups only the subfoveolar choroidal thickness was significantly different, which was significantly higher in the 1st and the 2nd groups and quite higher in patients with severe COVID-19 course (Fig. 3, Table 2).

Similar pattern was discernible with the diameter of peripapillary vessels, the increase in diameter of which turned out to be proportional to the disease's severity degree. More exact diameter change could be traced for the MAD index, but the MVD of patients wit severe COVID-19 course was 20 μm higher than that in the control group ($p < 0.001$).

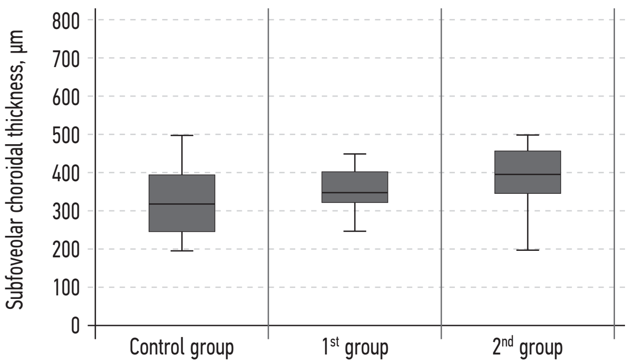

Fig. 3. The thickness of the choroid in the subfoveolar region in patients of different groups

Рис. 3. Толщина хориоидеи в субфовеолярной области у пациентов разных групп

Table 2. The main morphometric parameters of the examined groups, *Me* [min; max]

Таблица 2. Основные морфометрические показатели обследуемых групп, *Me* [min; max]

Index	Control group (C)	1st group	2nd group	$p_{C\ and\ 1}$	$p_{1\ and\ 2}$
Macular thickness in the foveal area, μm	274 [211; 305]	272 [211; 305]	270 [211; 305]	.977	.642
Mean neuroretinal rim thickness, μm	313 [239; 360]	301 [227; 409]	304 [201; 385]	.553	.929
Mean retinal nerve fiber layer thickness, μm	96 [83; 115]	97 [78; 114]	97 [87; 105]	.856	.858
Subfoveolar choroidal thickness, μm	308 [191; 483]	344 [248; 441]	392 [211; 502]	.001	.001

Note. $p_{C\ and\ 1}$ — statistical significance of differences between the control group and the 1st group (Mann–Whitney test); $p_{1\ and\ 2}$ — statistical significance of differences between the 1st group and the 2nd group (Mann–Whitney test)

Table 3. Thickness of peripapillary arteries and veins, diameter of their lumen in the examined groups, *Me* [min; max]

Таблица 3. Показатели толщины перипапиллярных артерий и вен, диаметр их просвета в обследуемых группах, *Me* [min; max]

Index	Group	Mean vessel diameter, μm		Mean ratio of the lumen of vessels to their diameter, %	
Peripapillary arteries	Control	67.2 [56.0; 84.6]	$p = 0.010$, $p = 0.003$	55.6 [34.2; 73.1]	$p = 0.804$, $p = 0.952$
	1st group	75.2 [62.1; 95.0]		58.6 [32.8; 63.9]	
	2nd group	82.3 [55.2; 101.8]		56.2 [35.2; 62.5]	
Peripapillary veins	Control	99.2 [81.5; 144.0]	$p = 0.317$, $p < 0.001$	62.7 [27.3; 87.5]	$p = 0.773$, $p = 0.911$
	1st group	102.0 [78.5; 127.5]		67.0 [34.7; 78.0]	
		119.1 [95.3; 139.2]		66.7 [33.4; 84.2]	

Note. Significance values are shown for the Mann–Whitney test in pairs between two independent samples.

In spite of a significant change of the peripapillary vessel diameter, indices of vessel diameter ratio to the diameter of its lumen did not have any significant differences between studied groups, namely the diameter of vessels' lumen increased proportionally to the increase of their complete diameter (Table 3, Fig. 4).

Significant positive correlations were revealed between indices of choroidal thickness and the peripapillary vessel diameter in the 1st and the 2nd groups of patients. For MAD, correlation coefficients were not higher than 0.4 — totally in the 1st and the 2nd groups, $r = 0.389$, $p < 0.001$. The most powerful positive correlation could be traced for MVD value in the 1st and the 2nd groups of patients ($r = 0.584$; $p < 0.001$) (Fig. 5).

Estimating the parameters of the capillary endothelium's glycocalyx, correlations were revealed with the MVD of patients with severe COVID-19 course. The most significant out of them appeared to be a

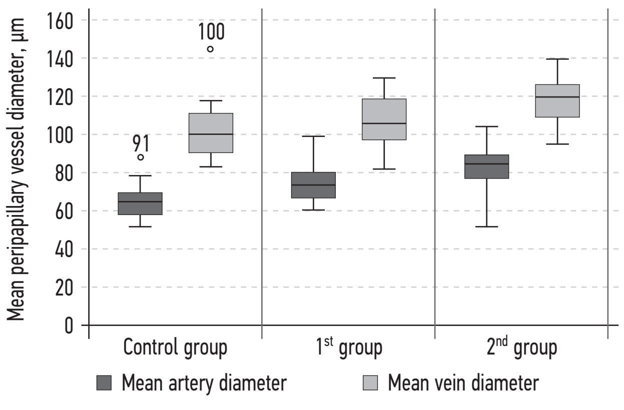

Fig. 4. Average values of the peripapillary arteries and veins thickness in the examined groups

Рис. 4. Средние показатели толщины перипапиллярных артерий и вен в обследуемых группах

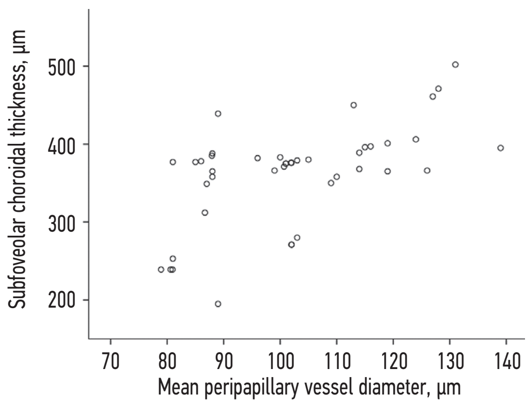

Fig. 5. Distribution diagram of the average thickness of the choroid and MVD in groups 1 and 2

Рис. 5. Диаграмма распределения средних показателей толщины хориоидеи и среднего диаметра вен в 1-й и 2-й группах

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Table 4. Spearman rank correlation coefficients between MDV and MAD and VEGLX scores in the main groups

Таблица 4. Коэффициенты ранговой корреляции Спирмена между средним диаметром вен и средним диаметром артерий и показателями VEGLX в основных группах

Index	Control group		1st group		2nd group	
	MAD	MVD	MAD	MVD	MAD	MVD
RBC filling, %	.128 (*p* = 0.570)	.037 (*p* = 0.871)	–.056 (*p* = 0.710)	.257 (*p* = 0.084)	–.324 (*p* = 0.054)	**–.587 (*p* < 0.001)**
RBP of 5–25 μm capillaries	.245 (*p* = 0.272)	–.013 (*p* = 0.953)	.022 (*p* = 0.888)	–.116 (*p* = 0.453)	.098 (*p* = 0.569)	**.468 (*p* = 0.04)**
RBP of 5–9 μm capillaries	–.154 (*p* = 0.493)	–.023 (*p* = 0.920)	.029 (*p* = 0.482)	–.188 (*p* = 0.222)	.115 (*p* = 0.505)	**.385 (*p* = 0.020)**
RBP of 10–19 μm capillaries	.174 (*p* = 0.440)	–.030 (*p* = 0.893)	–.021 (*p* = 0.892)	–.220 (*p* = 0.151)	.041 (*p* = 0.814)	**.387 (*p* = 0.020)**
RBP of 20–25 μm capillaries	.285 (*p* = 0.198)	–.069 (*p* = 0.762)	.054 (*p* = 0.730)	.152 (*p* = 0.325)	.164 (*p* = 0.338)	**.479 (*p* = 0.003)**
MicroVascular Health Score	–.025 (*p* = 0.918)	–.362 (*p* = 0.116)	.116 (*p* = 0.488)	–.150 (*p* = 0.368)	–.286 (*p* = 0.101)	–.273 (*p* = 0.118)

Note. Significant correlations are put in bold. MAD — mean artery diameter; MVD — mean vein diameter; RBC filling — index of capillary filling with red blood cells; RBP — density of the limiting perfusion area.

Table 5. Correlations between retinal vein diameter, choroidal thickness, and laboratory parameters in patients with severe COVID-19

Таблица 5. Корреляции между диаметром ретинальных вен, толщиной хориоидеи и лабораторными показателями пациентов с тяжёлым течением COVID-19

Index	MAD	MVD	Choroidal thickness	RHFL thickness
Level of leucocytes	.013	.504, *p* < 0.001	.562. *p* < 0.001	.502
ESR	–.351	.656, *p* < 0.001	.363	–.601
D-dimer	.578, *p* < 0.001	.564, *p* < 0.001	.277	.133
Fibrinogen	–.292	.067	–.004	.611, *p* < 0.001
Prothrombin	.377	.615, *p* < 0.001	.662, *p* < 0.001	.722, *p* < 0.001
Ferritin	.518	–.369	.651, *p* < 0.001	.179

Note. MAD — mean artery diameter; MVD — mean vein diameter; RNFL — retinal nerve fiber layer.

negative moderate correlation of MVD with RBC filling — the filling of small capillaries with red blood cells ($r = -0.587$; $p < 0.001$), as well as a positive correlation between MVD and the density of the limiting perfusion RBP in large 20–25 μm capillaries ($r = 0.479$; $p < 0.001$) (Table 4).

At comparison of data, obtained by ophthalmoscopic examination of patients with laboratory tests' results significant correlations were found with ocular blood flow parameters in the group of patients with a severe COVID-19 course. Some moderate positive correlations are revealed between retinal MVD and white blood cell level ($r = 0.504$; $p < 0.001$), erythrocyte sedimentation rate value ($r = 0.656$; $p < 0.001$), D-dimer value ($r = 0.564$; $p < 0.001$) and prothrombin value ($r = 0.615$; $p < 0.001$). The D-dimer value also positively correlated with the MAD of the retina in this group of patients ($r = 0.578$; $p < 0.001$). The choroidal thickness was in average higher in patients with higher leucocyte level in blood ($r = 0.562$; $p < 0.001$), prothrombin level ($r = 0.662$; $p < 0.651$), and ferritin level ($r = 0.504$; $p < 0.001$) (Table 5, Fig. 6).

DISCUSSION

At the course of the investigation, data were obtained characterizing morphometric retinal and choroidal parameters in patients within 3 months after at its moderate severity and severe course.

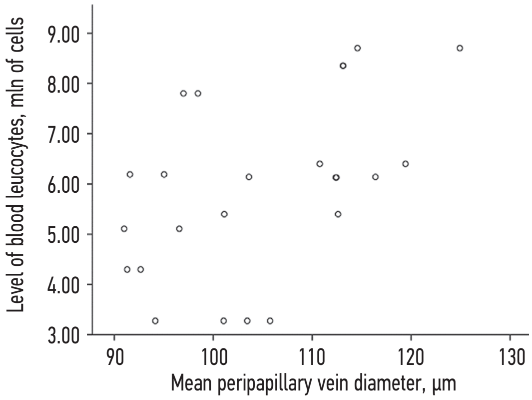

Fig. 6. Distribution of MVD and white blood cell count in patients with COVID-19
Рис. 6. Распределение среднего диаметра вен и уровня лейкоцитов у пациентов с COVID-19

Significant increase was noticed in the choroidal thickness and the diameter of peripapillary arteries and veins, which was proportional to the severity degree of the disease. Most prominent increase in choroidal thickness in the subfoveolar area and the increase in retinal vein diameter was revealed in patients with severe infection course.

Of special note is that in patients after COVID-19 during the sub-acute period, namely the enlargement of retinal vessels (vasodilatation) was observed, but not the vessel wall thickening, as evidenced by the fact that the ratio of the vessel diameter to its lumen diameter was preserved.

The phenomenon of retinal vessel diameter increase associated with coronavirus infection was already time and again confirmed by descriptions of the ophthalmoscopic aspect of the disease and found its confirmation in measurement of vessel diameters [8, 18]. It was expected that this happens as a result of the vascular wall thickening [19].

Relations revealed as a result of the present study between the increase in choroidal thickness, diameter of retinal arteries and veins, and laboratory biomarkers of systemic inflammation and hypercoagulation might indicate an inflammatory cause of microangiopathy.

The examination of vascular endothelial glycocalyx (VEGLX) in patients after a coronavirus infection, — is a new and to our opinion, advanced direction. It is known that the main glycocalyx functions are barrier, mechanic-sensory, regulatory (regulates among others the adhesion of immune competent cells), and "reservoir" one (area of fixation and storing of biologically active molecules) [16]. The endothelial glycocalyx structure impairment directly reflects the state and the functional activity of the vascular endothelium. VEGLX in principle does not have any differences in capillaries of different organs. Elucidated in the present study decrease in PBR density and lower level of capillary filling with red blood cells (RBC filling) in the sublingual plexus, which correlate with retinal vessel diameter, offer the opportunity of direct relation between microcirculatory disturbances in the retina and systemic endotheliopathy in patients after coronavirus infection.

Nowadays, it is still unclear whether these changes are reversible or irreversible. Some studies testify that parameters of choroidal thickness and peripapillary vessel diameter at a later period show no significant differences from those of the control group [20–24]. At the same time, a tendency to retinal thinning related to the decrease in vascular density in the superficial and deep capillary plexuses, enlargement of the avascular zone, impairment of perfusion indices during the post-covid period allows to suggest that retinal microangiopathy leads to chronic subclinical micrcirculatory disturbances [22, 25].

The present study has some limitations. To such belong relatively small sample size and absence of the possibility, at "red zone" conditions, of additional detailed examination of retinal blood flow using fluorescein angiography and OCT-angiography methods. But as the most important limitation, one could consider the impossibility of taking into consideration the influence of systemic therapy on obtained data. All patients received therapy both during COVID-19 and post-infection period, including terms of ophthalmic examination. Medical therapy (antiviral, antiinflammatory, hypotensive, antiarrythmic, etc.) did not allow to completely exclude the influence on the retinal vessels' diameter and on the choroidal thickness, as well as on the glycocalyx status. However, the uniformity of studied groups, including age and concomitant diseases to our opinion minimized the risks of the study bias.

CONCLUSIONS

1. In patients after moderate severity and severe COVID-19 infection, during the convalescence period (up to 30 days), an increase in peripapillary vessel diameter and in choroidal thickness has been observed.

2. The retinal vessel enlargement in coronavirus infection is not accompanied by ratio change of the diameter of arteries/veins to the diameter of their lumen. Because if this, one may talk of their vasodilatation.

3. Vasodilatation of retinal vessels and increase in choroidal thickness are proportional to the COVID-19 severity degree, laboratory markers of systemic inflammation and hypercoagulation (leucocyte number, erythrocyte sedimentation rate value, D-dimer and prothrombin levels), which is evidence of inflammatory origin of changes.

4. The degree of post-Coivid retinal microangiopathy correlates with indices indicative of the thickness impairment of the endothelial glycocalyx in the sublingual capillary plexus; this indirectly speaks for the connection with systemic COVID-19-associated endotheliopathy.

CONCLUSION

Morphometric changes of retinal vessels may play a role of a new biomarker, reflecting the severity of the COVID-19-associated systemic endotheliopathy.

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