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PATTERNS OF PROGRESSION OF DIABETIC RETINOPATHY DUE TO CORONAVIRUS INFECTION ACCORDING TO OCT-ANGIO.

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Abstract. The purpose of study. To study the progression patterns of diabetic retinopathy (DR) based on OCT-angio data. Methods. A total of 54 patients with DR were included in the study based on the selection results. The work included an in-depth ophthalmological examination of patients using general and special methods included in the standard for examining patients with DR. Data from a previous (2019) ophthalmological examination and data on past COVID-19 were retrospectively studied. OCT-angio was performed to clarify the stage of DR and monitor the dynamics of its progression. Patients included in the study groups had data from a previous OCT-angio, which was performed as part of an ophthalmological examination prior to undergoing COVID-19. Results. The analysis was carried out in 2 comparative groups depending on the progression of DR. Analysis of the severity of DR in the eyes of patients in whom disease progression was detected (n=36) showed that in 66,7% of cases the general disease of COVID-19 proceeded in a severe form, in 22,2% - in a moderate form and in 11,1% of cases - in a mild form. In patients with DR in the study group, on average, there was a significant increase in the foveal avascular zone (FAZ) after coronavirus infection (by 24,5-61,5% above the norm (p<0.05)). Qualitative analysis showed signs of rupture of the perifoveolar vascular ring and impoverishment of the perifoveolar vascular pattern. The results of a group of patients with progression of DR showed that after a coronavirus infection, a statistically significant (p<0.05) decrease in blood flow density in the macular zone was found in almost all areas of the study. Conclusion. The following indicators can be considered as OCT-angio biomarkers of DR progression against the background of coronavirus infection: a decrease in the area of the FAZ and a decrease in blood flow density in the macular zone with a decrease in the average value for 9 quadrants by more than 2 times.

Key words: coronavirus infection; COVID-19; diabetic retinopathy; OCT- angio; progression patterns.

Introduction. Diabetic retinopathy (DR) is currently one of the most common pathologies of the eye fundus, leading to vision loss in people of working age [1,2]. At the same time, patients with diabetes mellitus (DM) are one of the most vulnerable groups in relation to coronavirus infection. There are a large number of publications that report a more severe course of the disease in patients with DM and its complications, and therefore it is considered one of the most significant comorbidity factors in patients along with obesity [3,4,5,6].

The impact that coronavirus infection has on the course of DR deserves special attention, since the pathogenesis of this complication is closely related to vascular

damage, impaired hemostasis, and the development of ischemia. All of the listed pathological processes are integral components of the pathological process in COVID-19 [7,8]. Patients with DR need regular monitoring of the state of the fundus, which became much more difficult during the pandemic, as the introduction of restrictive measures affected the normal operation of ophthalmological institutions. As a result, patients were left without special supervision by ophthalmologists for a long time, and many of them managed to endure the disease, most of them in severe form against the background of long-term use of drugs that affect hemostasis and glycemic profile, which could not but affect the course of DR [9,10].

An important factor in the course of COVID-19, which can influence the course and progression of DM and DR, should be considered developing coagulopathy and vasculitis. In the scientific literature, the collective term thrombovasculitis is more popular. The influence of these pathological processes in the pathogenesis of DR is hard to deny, since the main trigger factor in the development of the main manifestations of DR is ischemia. Thrombovasculitis in this case is an indisputable factor that can aggravate ischemia of retinal tissues, increase vascular permeability and promote the development of neovascularization [11,12,13].

In connection with the above, the study of the effect of coronavirus infection on the course and progression of DR and the determination of criteriathat indicate the relationship between these two pathological processes is of great scientific and practical interest.

Purpose of the study. Study of biomarkers of progression of diabetic retinopathy based on OCT-angio data.

Material and research methods. The study was conducted on the basis of the Termez branch of the Republican Specialized Scientific and Practical Medical Center for Eye Microsurgery from July 2020 to August 2021.

The criteria for inclusion of patients in the study were:

- the presence of a diagnosis of DR confirmed by the data of an ophthalmological examination;
- availability of data on the ophthalmological examination performed on the territory of the institution where the work was performed in 2019;
- confirmed by the results of immunological (ELISA, PCR) or instrumental (MSCT of the chest) methods, the diagnosis of transferred COVID-19;
- availability of laboratory test results (general blood analysis, biochemical blood test, coagulogram) and data on received treatment for COVID-19;
- the presence of a subjective sensation of decreased vision in a patient after undergoing COVID-19.

(108 eyes) were included in the study. The mean age of the patients was 56,6±6,3 years. The gender distribution was as follows: 21 male (38,9%) and 33 female (61,1%). All patients suffered from type 2 DM with an experience of 3 to 12 years.

The most common comorbidities in patients were also: hypertension (90,7%), coronary heart disease (83,3%) and obesity (92,6%).

The work included an in-depth ophthalmological examination of patients using general and special methods included in the standard for examining patients with DR. Data from a previous (2019) ophthalmological examination and data on past COVID-19 were retrospectively studied.

OCT-angio technique. OCT-angio was performed to clarify the stage of DR and monitor the dynamics of its progression. The study was performed on an Optopol Technology Revo (SOCT Copernicus REVO/ REVO NX) device (Poland) in the Angio Retina mode with a scanning area of 3×3 mm.

The study assessed the density of the capillary network of the superficial vascular plexus in 9 quadrants: superior temporal, superior, superior nasal, nasal, central, temporal, inferior temporal, inferior nasal, as well as in the foveal and parafoveal

zones.

The value of microcirculation density was expressed in%. The area of the foveal avascular zone (FAZ) was also evaluated, expressed in mm2.

Patients included in the study groups had data from a previous OCT, which was performed as part of an ophthalmological examination prior to undergoing COVID-19.

Statistical data processing. Statistical processing of the data of the studied patients was carried out using the Microsoft Office Excel 2019 software package (Microsoft Corp., USA) and STATISTICA 13 (StatSoft Inc., USA). When comparing two independent samples with a normal distribution of indicators, Student's t-test was used. Differences were accepted as statistically significant at $p<0.05$.

Results.

ETDRS classification (1991) was used to classify the stages of DR. Table 1 shows the distribution of patients with DR depending on the stage according to the results of the ophthalmological examination in 2019 before the illness of COVID-19 and after the illness.

One of the criteria for inclusion of patients in the study was the appearance of complaints of decreased vision after suffering COVID-19. However, despite this, the data of an in-depth ophthalmological examination revealed the progression of the DR stage only in 36 eyes (33,3%).

At the same time, the analysis showed that the progression of the stages of non-proliferative retinopathy prevailed in people who underwent COVID-19. In most cases, there was a transition of the initial stage of non-proliferative retinopathy to moderate and moderate to severe. That is, according to the classification criteria of ETDRS (1991), was a progression of such ophthalmoscopic symptoms of DR as microaneurysms, microhemorrhages, intraretinal microvascular anomalies, and clear venules. The development of neovascularization, fibrosis, preretinal or vitreal hemorrhage, indicating the transition to the proliferative stage or its progression, was observed relatively less frequently. In 4 eyes (3,7%) of patients, there were cases of transitions from an advanced stage of DR to a stage when gradation is impossible due to the fact that there is no possibility to perform an ophthalmoscopy of the fundus.

Table 1.

Distribution of patients with DR by stages (ETDRS, 1991) before and after coronavirus infection.

Stage of DR	Before COVID-19 (2019)	After COVID-19 (2020-2021)
No retinopathy	8(7,4%)	2(1,9%)
Initial non-proliferative	8(7,4%)	6(5,6%)
Moderate non-proliferative	9(8,3%)	10(9,3%)
Pronounced non-proliferative	9(8,3%)	12(11,1%)
Severe non-proliferative	17(15,7%)	18(16,7%)
Initial proliferative	20(18,5%)	20(18,5%)
Expressed proliferative	10(9,3%)	12(11,1%)
Severe non-proliferative (risk A)	8(7,4%)	9(8,3%)
Severe non-proliferative (risk B)	9(8,3%)	9(8,3%)
Far advanced proliferative	10(9,3%)	6(5,6%)
Gradation not possible	-	4(3,7%)
Total	108(100%)	108(100%)

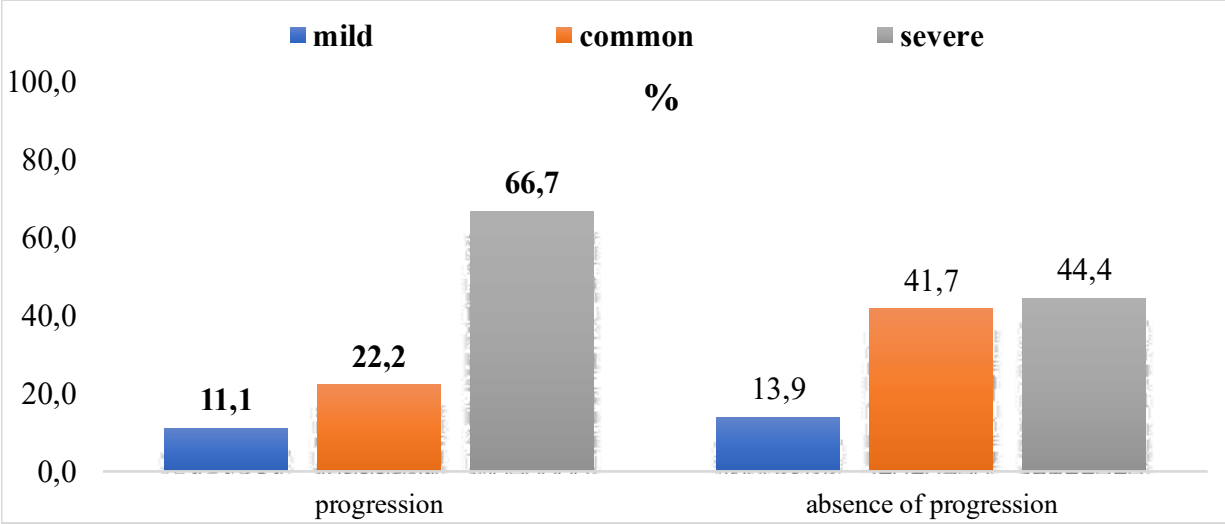


Figure 1. Distribution of patients with DR according to the severity of COVID -19.

Subsequently, the analysis was carried out in 2 comparative groups, depending on the progression of DR. Analysis of the severity of DR in the eyes of patients in whom disease progression was detected (n=36) showed that in 66,7% of cases the general disease of COVID-19 proceeded in a severe form, in 22,2% - in a moderate form and in 11,1% of cases - in a mild form (Fig. 1).

In the eyes of patients in whom the stage of the disease did not progress (n=72), the proportion of patients with severe and common forms of the disease was approximately equal, amounting to 44,4% and 41,7%, respectively. The proportion of patients with mild disease was 13,9%.

Study of biomarkers of DR progression in patients after coronavirus infection based on OCT-angio. At a further stage of the study, patients, depending on the established fact of progression, were divided into 2 groups: the study group consisted of patients with progression of DR, and the comparative group consisted of patients with no progression of DR.

The results of the study of FAZ in the study groups are presented in Figure 2. The data of the graph show that in both groups of patients there was an increase in the average FAZ and an expansion of the ranges of values after undergoing COVID-19. At the same time, in the study group, the increase in the indicator was more pronounced.

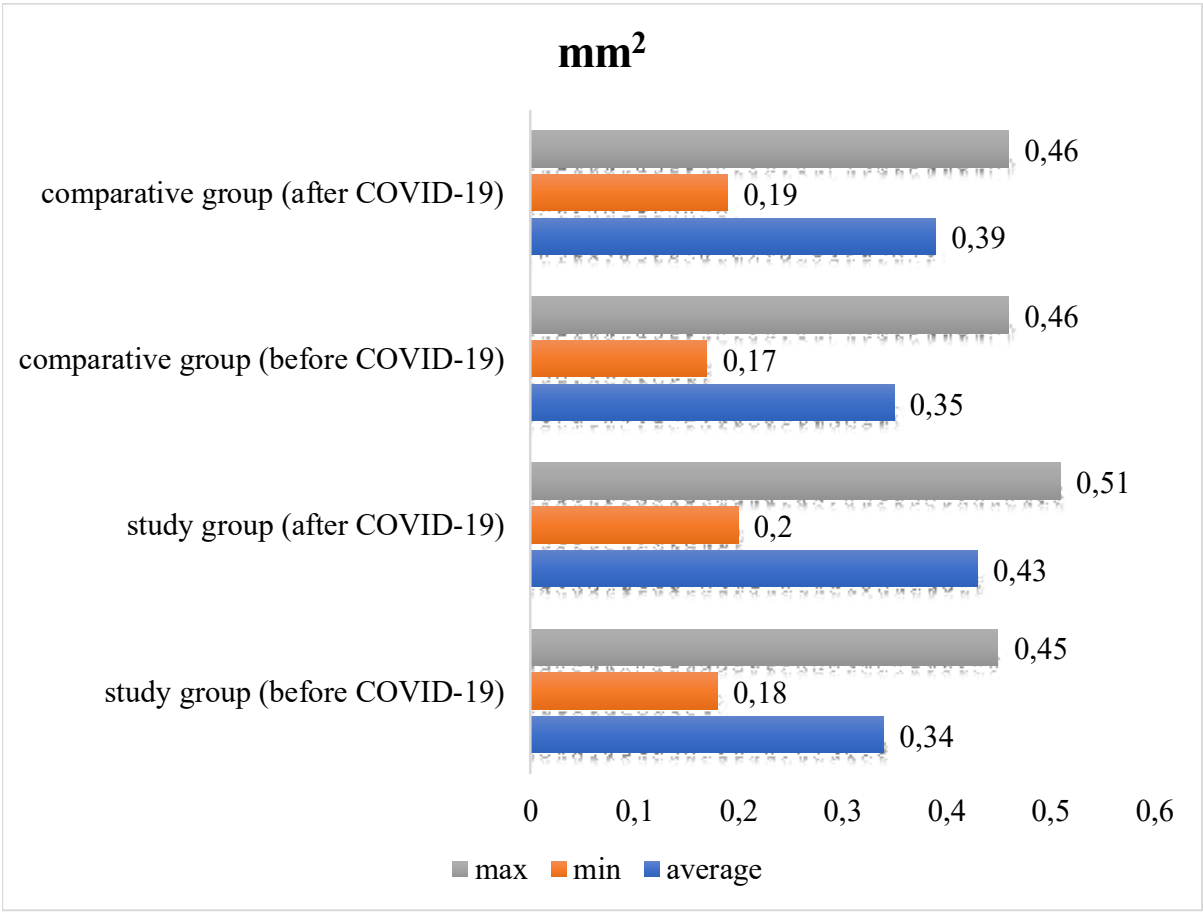


Figure 2. Dynamics of the indicator of the size of the FAZ in the studied groups (mm2).

In patients with DR in the study group, on average, there was a significant increase in the FAZ after coronavirus infection (by 24,5-61,5% above the norm ($p<0.05$)). Qualitative analysis showed signs of rupture of the perifoveolar vascular ring and impoverishment of the perifoveolar vascular pattern.

Tables 2 and 3 present the results of the analysis of the dynamics of blood flow density in the macular zone in dynamics before and after the coronavirus infection in patients in groups with and without progression of DR.

Table 2.

Dynamics of blood flow density in the macular zone in a group of patients with no progression of DR (n=72), scanning area 3x3 mm.

Research Zones	Reference values	Before COVID-19	%*	After COVID-19	%*
Superior temporal	49,31±1,01	48,2±1,11	2,3	46,2±1,84	6,3
Upper	54,38±0,96	52,2±1,23	4,0	49,5±1,24 ^	9,0
superior nasal	55,57±0,75	52,6±1,45	5,3	51,2±1,05	7,9
nasal	57,61±0,77	53,1±1,32	7,8	52,3±1,33	9,2
Central	52,62±0,51	50,1±0,89	4,8	51±1,6	3,1
temporal	54,43±0,65	52,7±1,27	3,2	51,3±1,88	5,8
Inferotemporal	51,77±1,12	50,3±2,1	2,8	48,9±1,76	5,5
Lower	54,06±0,71	52,6±1,2	2,7	50,6±1,84	6,4
Infero-nasal	56,21±0,78	54,2±0,96	3,6	53,2±1,24	5,4
Average of 9 quadrants	54,0±0,57	51,5±1,8	4,6	50,6±0,96	6,3
Fovea + parafovea zone	54,02±0,61	54,4±1,78	0,7	53,3±1,45	1,3
fovea	33,48±1,96	31,1±1,16	7,1	30,2±1,78	9,8
parafovea zone	56,78±0,58	54,8±2,12	3,5	53,5±1,35	5,8

* - percentage of deviation from reference values; ^ - differences in comparison with the average values before undergoing COVID -19 are statistically significant at $p < 0.05$.

The results of the group of patients without progression of DR showed that, despite the established decrease in blood flow density in the macular zone in almost all areas of the study, the differences in comparison with the indicators before the coronavirus infection were statistically significant ($p<0.05$) only in the upper quadrant. At the same time, the percentage of deviation from the reference values of the average value for 9 quadrants before the coronavirus infection was 4,6%, and after the infection, this figure was 6,3%. A similar picture was observed in relation to the percentage of deviation from the norm in terms of the fovea and parafovea zones (Table 2).

The results of the group of patients with progression of DR showed that after a coronavirus infection, a statistically significant ($p<0.05$) decrease in blood flow density in the macular zone was found in almost all areas of the study.

Table 3

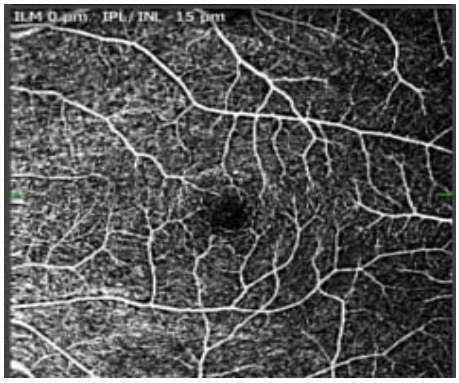
Dynamics of blood flow density in the macular zone in a group of patients with progressive DR (n=36), scanning area 3x3 mm.

Research Zones	Reference values	Before COVID-19	%*	After COVID-19	%*
Superior temporal	49,31±1,01	47,7± 1,02	3,3	45,8±1,23	7,1
Upper	54,38±0,96	51,8±0,84	4,7	49,1±1,01	9,7
superior nasal	55,57±0,75	52,2±1,12	6,1	49,9±0,96	10,2
nasal	57,61±0,77	53,4±0,98	7,3	46,8±0,88^	18,8
Central	52,62±0,51	50,9±0,87	3,3	44,6±1,12^	15,2
temporal	54,43±0,65	52,5±1,13	3,5	47,8±1,23^	12,2
Inferotemporal	51,77±1,12	49,8±1,2	3,8	44,5±0,97^	14,0
Lower	54,06±0,71	52,3±0,95	3,3	48,9±1,15^	9,5
Infero-nasal	56,21±0,78	53,5±1,43	4,8	51±1,24	9,3
Average of 9 quadrants	54,0±0,57	51,7±1,56	4,3	48,2±0,97	10,7
Fovea + parafovea zone	54,02±0,61	53,8±1,43	0,4	48,4±1,25^	10,4
fovea	33,48±1,96	30,4±0,97	9,2	28,5±1,12	14,9
parafovea zone	56,78±0,58	54,5±1,53	4,0	48,9±1,26^	13,9

* - percentage of deviation from reference values; ^ - differences in comparison with the average values before undergoing COVID -19 are statistically significant at p <0.05.

At the same time, the percentage of deviation from the reference values of the average value for 9 quadrants after the coronavirus infection was 10,7%, while before the infection, this figure was only 4,3% (Table 3).

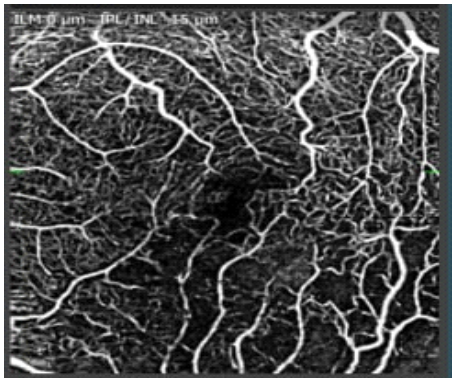
Figure 4 shows clinical examples of various stages of DR in patients with coronavirus infection, which depict FAZ during an OCT-angio study. The images clearly demonstrate that with the progression of the stage of DR, the area of the macular FAZ progressively increases, which indicates an increase in the degree of ischemia of the retinal tissue.



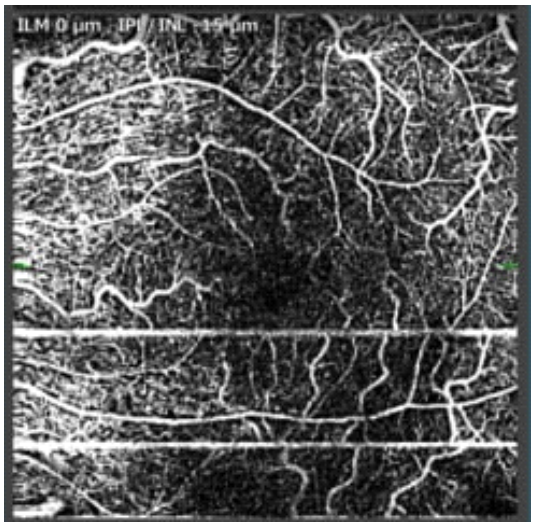
OCT-angio of a patient with an initial non-proliferative stage of DR:

a slight rupture of the perifoveolar capillary ring is determined, slight and

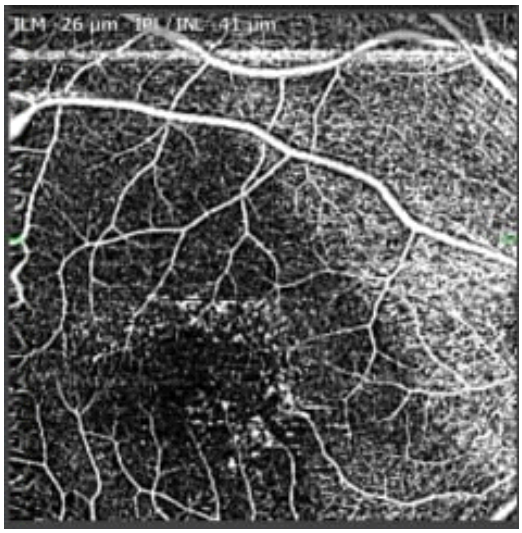
areas of depleted blood flow in all quadrants with an FAZ area of 0.180 mm2



OCT-angio of a patient with a severe non-proliferative stage of DR, FAZ expansion and depletion of blood flow are determined mainly in the fovea and parafovea zone with a FAZ area of 0.252 mm2



OCT-angio of a patient with the initial proliferative stage of DR, there is an extensive expansion of the FAZ, rupture of the perifoveolar capillary ring and depletion of blood flow to a greater extent in the fovea and parafovea zone and to a lesser extent - with a FAZ area - 0,402 mm2



OCT-angio of a patient with severe proliferative stage of DR, pronounced expansion of the FAZ, rupture of the perifoveolar capillary ring, areas of lack of blood flow in the fovea and parafovea zone, as well as depletion of blood flow in all quadrants, FAZ area - 0.528 mm2

OCT-angio of a patient with the initial proliferative stage of DR, there is an extensive expansion of the FAZ, rupture of the perifoveolar capillary ring and depletion of blood flow to a greater extent in the fovea and parafovea zone and to a lesser extent - with a FAZ area - 0,402 mm2 OCT-angio of a patient with severe proliferative stage of DR, pronounced expansion of the FAZ, rupture of the perifoveolar capillary ring, areas of lack of blood flow in the fovea and parafovea zone, as well as depletion of blood flow in all quadrants, FAZ area - 0.528 mm2

Figure 4. Clinical examples of FAZ images on OCT-angio in patients with DR due to coronavirus infection.

Discussion. In patients with diabetic retinopathy (DR), biomarkers can be used for the purpose of early diagnosis and prognosis of the disease, clarifying the stage of the process, monitoring the course, progression and recurrence. Also, biomarkers provide valuable information about the direction of therapy, the need to change its strategy, and also allow monitoring the safety of treatment [9,12,14].

Fluorescein angiography (FAG) is the main method for studying retinal perfusion, which serves as the main biomarker of the ischemic process, and in this regard, FA continues to be the "gold standard" for studying the vascular bed in DR. However, this study has a number of limitations related to the duration and the need for intravenous contrast, which can cause allergic reactions. In this regard, this research method is not suitable for screening and multiple repetitions [10,15,16].

OCT-angio is an innovative, non-invasive and reproducible high-resolution imaging technique for microcirculation in the retina that allows for the isolation of superficial and deep retinal vascular plexuses. OCT-angio also allows quantitative analysis of retinal vascular changes. The data obtained using the method of optical coherence tomography in the angiography mode (OCT-angio) are the so called visualized biomarkers, that is, these are biomarkers determined on images [4,6,8,12].

Studies show that the results obtained using FAG and OCT-angio, in general, repeat each other in terms of assessing the area of ischemia and neovascularization. However,

there are some differences in the data. For example, with OCT-angio, not all areas with neovascularization visible on FAG are determined, since OCT-angio does not reflect the process of leakage of contrast from newly formed vessels. At the same time, OCT-angio makes it possible to determine the deep peri papillary vascular plexus and small areas of retinal neovascularization, which are not always determined using FAG [2,6,14].

Conclusion.

Thus, according to the results of the study, it was found that cases of progression of DR in patients with coronavirus infection are characterized by significant microcirculation disorders in the macular zone of the retina, which can be objectively detected using the OCT-angio method. The following indicators can be considered as OCT-angio biomarkers of DR progression against the background of coronavirus infection: a decrease in the area of the foveolar avascular zone and a decrease in blood flow density in the macular zone in the following main zones: nasal, lower temporal and central (foveal and parafoveal zone) with a decrease in the average indicator for 9 quadrants more than 2 times.

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