An account of retinal microvascular changes in diabetes acquired by OCT-angiography

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*The **Purpose** of this work was to determine microvascular changes in the macular zone with diabetes mellitus (DM) and with different stages of diabetic retinopathy (DR) using optical coherence tomography angiography (OCT-A). **Materials and methods.** 60 patients were inspected (109 eyes) between the ages 58.2 ± 3.27 with DM (patients without clinical DR and with different stages of DR). The control group consisted of 75 healthy subjects (150 eyes) and was compared by gender and age to the DR group. OCT-A was performed with the help of the instrument RTVue XR Avanti (Optovue Inc, USA) in the Angio Retina settings with the scanning field dimensions 3 x 3 mm and 6 x 6 mm. The density of the top vascular plexus in the capillary network was evaluated in 9 quadrants, in the foveal and parafoveal zones, and in the foveal avascular zone (FAZ). **Results.** In patients with D, all groups were observed to have a significantly decreased density in blood flow in the top capillary network and a widened FAZ in comparison with the control group. The decrease density of blood flow was more evident in groups with preproliferative diabetic retinopathy (prePDR) and with proliferative DR (PDR), averaging at 16.6 % / 13.6 % and 15.5 % / 7.5 % in scanning fields of 3 x 3mm / 6 x 6 mm, respectively. The FAZ field with DM and DR was at 38.5%, with nonproliferated DR – at 26.9 %, with prePDR – at 65.4 %, and with PDR at 30.8 % higher than the control group. **Conclusion.** OCT-A allowed the identity of microvascular changes within the macular zone with DM in even the most early stages of the disease, when there were no manifestations of DR at the eye's fundus. Early indicators of changes in the microcirculatory path of the retina with DM were qualitative and quantitative changes. These changes were within the FAZ and in the decreased density of the surfacevascular plexus in the capillary network within the scanning fields of 3 x 3 mm.*

Ключевые слова: diabetes, diabetic retinopathy, OCT-A, optical coherence tomography angiography, OCT-angiography.

Conflict of interests: there is no conflict of interests.

For citations: An account of retinal microvascular changes in diabetes acquired by OCT-angiography. Russian ophthalmological journal. 2017; 10 (2): 40–5. (in Russian)

doi: 10.21516/2072-0076-2017-10-2-40-45

Financial disclosure: No author has a financial or property interest in any material or method mentioned.

Diabetes mellitus (DM) is known as one of the most important health care problems of the modern world. In the last 10 years, the amount of those affected by DM in the world has increased more than twice and in the end of the year 2014, consisted of 387 million people [1–3]. According to the World Health Organization, by 2030, DM will take seventh place amongst the top causes of death in the world. The prevalence of DM and the severity of its complications, such as, diabetic retinopathy (DR), are defined to be of great medical social importance. DR is a formidable complication of DM and is one of the leading reasons for blindness and weakened vision in all age groups. This explains the relevance of research aimed at improving the quality of diagnosis, prognosis, and treatment of DR.

At the present time the main instrumental methods of diagnosis of DR are optical coherence tomography (OCT) and fluorescent angiography (FAG) [4].The FAG method is highly sensitive which allows to evaluate the localization and the size of ischemic zones and to identify areas of neovascularization in the posterior pole and in the periphery of the eye fundus [5]. The disadvantages of FAG include the invasiveness of the technique. The necessity of the intravenous injection of a contrast substance, which

can cause allergic reactions as severe as anaphylactic shock, imposes certain limitations on the application of the method. To this day, it is simply impossible to imagine retinology without the OCT method – a fast, accurate, non-invasive, and highly sensitive method which allows for a qualitative and quantitative assessment of the macular zone conditions. This method is widely and actively used for screening and monitoring patients with DR [6].

The evolution of OCT technology led to the appearance of a fundamentally new research method – OCT-angiography (OCT-A) – in 2014 [7]. With the help of OCT-A, it became possible to obtain an image of the eye's retinal vasculature noninvasively, without using a dye. The method is based on the principle of amplitude decorrelation, which is based on the analysis of the differences in the amplitudes that a laser beam reflects from the selected retinal point during repeated scans. The amplitude of the reflected light varies more strongly at points where fluid moves (the zone which corresponds to the inner part of the vessels where the red blood cells are actively moving). This way, OCT-A allows for the visualization of our own blood flow. In photographs, vessels with blood flow are highlighted in a separate color, allowing for the clear visualization of the structure, shape, density, and the occupied area of the vasculature. Such features are used to conduct qualitative and quantitative assessments of microcapillary blood flow. Quantitative characteristics include the density of the capillary vasculature per unit area and the area of the foveal avascular zone (FAZ). A vital new feature of this method is the ability to visualize the vascular network of the retina and optic disc nerve (ODN) layer by layer. By changing the position of the EnFace scan layer to oth er levels, information about the blood flow in a particular layer necessary for analysis can be obtained. The level of the location for scanning the layer is set in 4 modes (superficial vascular plexus, deep vascular plexus, outer layer of the retina, layer of choriocapillaries) [8]. Obtaining data on angio-architetonics of the retina and choroid by this noninvasive method is possible under frequent monitoring and is defining the scope of applications for this method in clinical practices with vascular eye diseases, in particular, with DR.

In foreign literature, there are single reports on the use of OCT-A in patients with DR. G. Cennamo et al. have shown the informative value of OCT-A in comparison with FAG in the diagnosis of ischemic maculopathy [9]. In a small pilot study, T. Hwang et al. recognized that the method was effective in assessing ischemic zones in the posterior pole with DM [10].

At this stage of development, the technical service provided by OCT-A can mainly be carried out in the posterior of the eye, which imposes certain limitations on the application of the method in studying DR; this method does not allow a full study of the state of the vascular bed at the periphery of the fundus. However, as the device improves technically with the development of the wide-field OCT-A, this limitation will be overcome.

The **PURPOSE** of this work is to use the OCT-A method to determine the microvascular changes within the macular zone with DM and at different stages of DR.

MATERIALS AND METHODS

60 patients (109 eyes) were examined. This included 28 males and 32 females 58.20 ± 3.27 years of age with DM, without clinical manifestations of DR and with nonproliferative (NPDR), preproliferative (prePDR), and proliferative (PDR) stages of DR. Visual acuity in the groups averaged 0.84 ± 0.05 (DM without DR – 1.0; NPDR – 1.0; prePDR – 0.55 ± 0.13; PDR 0.82 ± 0.08). The control group consisted of 75 healthy individuals (150 eyes) who were compared by gender and age with the target group. All patients underwent a standard ophthalmological examination. The stage of DR was determined on the basis of the clinical picture (including data from the examination of the fundus performed with the Goldman lens). In some cases, to check the stage of DR, FAG was conducted. OCT-A was performed with the help of RTVue XR Avanti (Optovue Inc, USA) in the Angio Retina mode with the scanning area 3 × 3 mm and 6 × 6 mm.The density of the top vascular plexus in the capillary network was evaluated in 9 quadrants (superior-temporal, superior, superior-nasal, nasal, central, temporal, inferior, inferior-temporal, inferior-nasal) and in the foveal and parafoveal zones. The value of the microcirculation's density was expressed as a percentage. The area of the foveal avascular zone (FAZ) was also measured and expressed in mm^2. On average, the thickness of the retina in the fovea was 265.72 ± 10.89 μm.

The study did not include patients with other eye diseases (initial cataracts and a refractive error of ±3.0 D were allowed) with clinically significant macular edema, eyes with PDR after vitrectomy with silicone present in the vitreal cavity. Also, scans with an image quality below 60 c.u. were excluded from the analysis, as a poor visualization of the fovea could lead to an artificial decrease in the density.

The statistical processing of the data was carried out using the MS Excel program.

RESULTS AND DISCUSSION

In all of the groups of patients with DM, there was a significant decrease in blood flow density in the surface capillary network and an expansion of FAZ compared to the control group.

In patients with DM, a significant increase in FAZ was observed on average compared with the control group ($p < 0.05$). The results of the study are presented in Table 1 and in Figure 1. The area of FAZ with DM and without DR was 38.5 %, with NPDR – 26.9 %, with prePDR – 65.4 %, with PDR – 30.8 % higher than the control group. With a qualitative analysis of the changes, attention was drawn to a rupture of the perifoveolar vascular ring which showed the depletion of the perifoviolar vascular pattern in patients with DM. The analysis of the morphometric indicators revealed that the size of the FAZ had significant

Table 1. The size of the foveal avascular zone in individuals with DM and with different stages of DR (mm^2)

Parameters	DM w/o DR	NPDR	prePDR	PDR	Control Group
Scanning zone 3 × 3 (M ± m)	0.36 ± 0.02	0.33 ± 0.02	0.43 ± 0.1	0.34 ± 0.02	0.2 ± 0.02
minimum	0.29	0.17	0.19	0.08	0.06
maximum	0.4	0.46	0.8	0.76	0.48
Scanning zone 6 × 6 (M±m)	0.34 ± 0.02	0.34 ± 0.03	0.45 ± 0.10	0.37 ± 0.03	0.27 ± 0.02
minimum	0.27	0.15	0.18	0.1	0.06
maximum	0.39	0.5	0.8	0.79	0.46

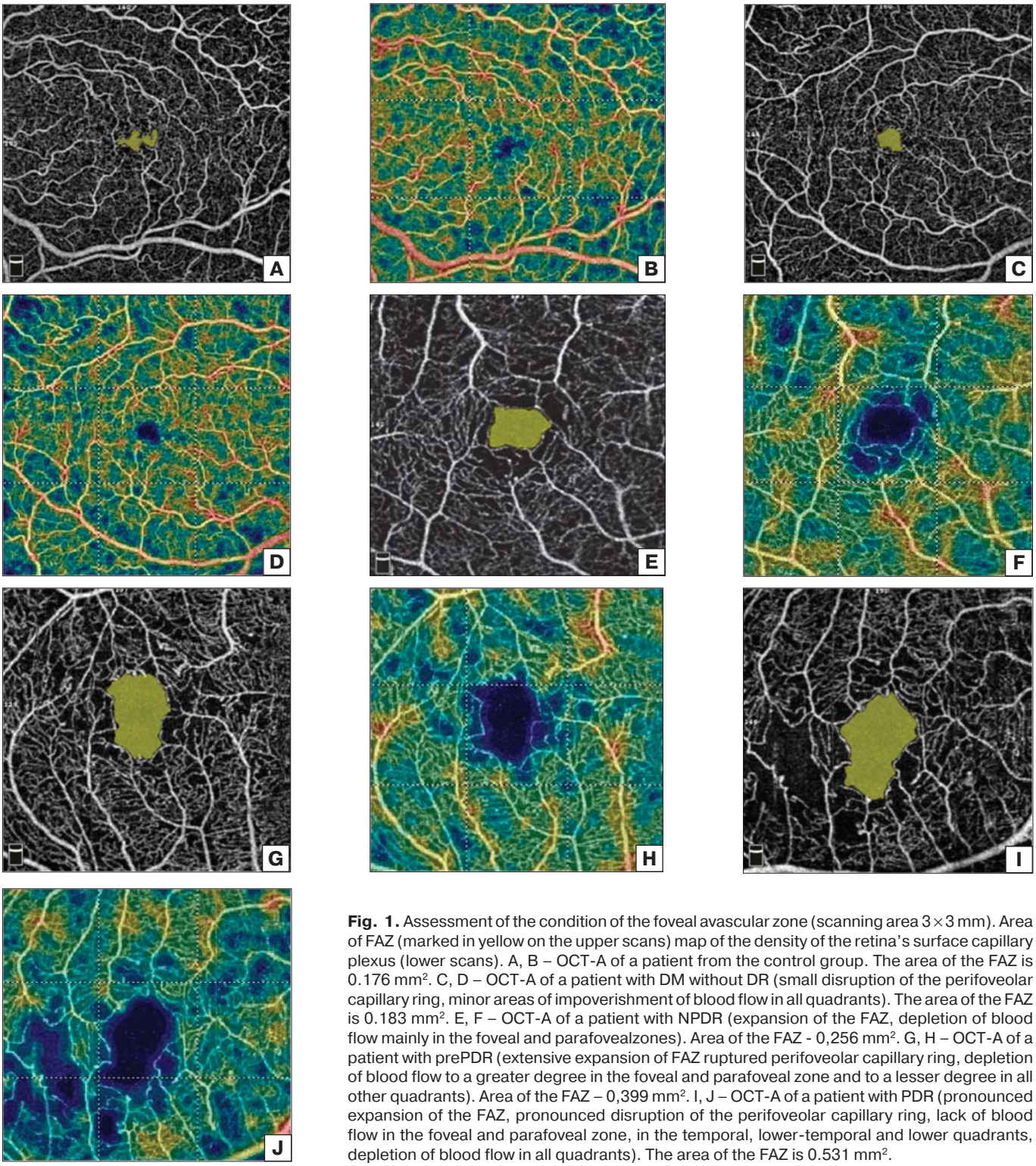

Fig. 1. Assessment of the condition of the foveal avascular zone (scanning area 3 × 3 mm). Area of FAZ (marked in yellow on the upper scans) map of the density of the retina's surface capillary plexus (lower scans). A, B – OCT-A of a patient from the control group. The area of the FAZ is 0.176 mm^2. C, D – OCT-A of a patient with DM without DR (small disruption of the perifoveolar capillary ring, minor areas of impoverishment of blood flow in all quadrants). The area of the FAZ is 0.183 mm^2. E, F – OCT-A of a patient with NPDR (expansion of the FAZ, depletion of blood flow mainly in the foveal and parafovealzones). Area of the FAZ - 0,256 mm^2. G, H – OCT-A of a patient with prePDR (extensive expansion of FAZ ruptured perifoveolar capillary ring, depletion of blood flow to a greater degree in the foveal and parafoveal zone and to a lesser degree in all other quadrants). Area of the FAZ – 0,399 mm^2. I, J – OCT-A of a patient with PDR (pronounced expansion of the FAZ, pronounced disruption of the perifoveolar capillary ring, lack of blood flow in the foveal and parafoveal zone, in the temporal, lower-temporal and lower quadrants, depletion of blood flow in all quadrants). The area of the FAZ is 0.531 mm^2.

individual variability. So, both in the control group and in the group with DM, patients with smaller sizes of FAZ (less than 0.1 mm^2) were noted, which appeared to be an individual trait/feature. At the same time, in the same examined groups, the maximum size of FAZ in healthy individuals was 0.48 mm^2, which was 1.6 times less than the maximum size of FAZ in patients with DR.

The study performed in Angio Retina mode with the 3 × 3 mm scanning area (Table 2, Figure 2) revealed that the group of patients with DM and without DR and HPDR had a less pronounced decrease in density averaging at 4–4.5 % compared to the control. However, the analysis of the quadrant data revealed that the maximum changes were observed in the central quadrant (15 % and 10 %, respectively) and in the foveal zone (19 % and 10 %, respectively). In the other quadrants, the decrease was less pronounced at 1–5 %. In the groups of patients with prePDR and PDR, the changes were more significant; the average decrease in blood flow density was 16.6 % and 15.5 %, respectively, with a uniform decrease in blood flow density across all quadrants.

The differences calculated in comparing all of the examined groups with the control group were highly reliable ($p < 0.05$), as well as in comparing the DM without DR and NPDR group with the pre PDR and PDR groups. There were no statistically significant differences between the DM groups without DR and NPDR and between the groups with prePDR and PDR.

With the 3 × 3 mm scanning area, the decrease in blood flow density in the central quadrant and in the foveal zone was associated with an increase in the FAZ size, which was already observed in the early stages of DR and even in DM without DR. With prePDR and PDR, the changes were more pronounced and were spread across all of the analyzed quadrant zones.

The results of the analysis of blood flow density with a 6 × 6 mm scanning area are presented in Table 3 and in Figure 3.

In all, the same trends were observed with a 6× 6 mm scanning area as when scanning with a 3 × 3 mm area, but these changes were less pronounced. In the group of patients with DM without DR, the indicators were practically no different from the control group. In addition, there was no decrease in the blood flow density in the

Table 2. The blood flow density in the macular zone of individuals with DM and in different stages of DR (%), scanning zone 3 × 3 mm

Zones Examined	w/o DR	%*	NPDR	%*	prePDR	%*	PDR	%*	Control Group
Superior-temporal	54.54 ± 0.43	2	53.96 ± 0.96	3	46.71 ± 1.99	16	47.87 ± 0.59	14	55.42 ± 0.37
Superior	56.43 ± 0.44	3	55.59 ± 1.04	4	47.09 ± 1.39	19	49.13 ± 0.76	15	58.03 ± 0.31
Superior-nasal	56.30 ± 0.64	3	55.99 ± 0.88	4	48.06 ± 1.74	17	49.91 ± 0.61	14	58.18 ± 0.34
Nasal	53.96 ± 0.45	5	53.94 ± 0.79	5	47.83 ± 1.51	16	46.77 ± 0.70	18	56.84 ± 0.31
Central	30.95 ± 1.39	15	32.51 ± 1.13	10	30.22 ± 1.74	17	30.54 ± 0.66	16	36.28 ± 0.66
Temporal	52.95 ± 0.29	4	53.08 ± 0.92	3	46.11 ± 1.83	16	45.88 ± 0.80	17	54.97 ± 0.32
Inferior-temporal	55.23 ± 0.41	1	53.48 ± 0.93	4	46.90 ± 1.79	16	47.07 ± 0.77	15	55.64 ± 0.39
Inferior	56.55 ± 0.46	2	55.73 ± 0.91	4	47.23 ± 2.09	19	47.58 ± 0.77	18	57.97 ± 0.34
Inferior-nasal	57.35 ± 0.55	1	55.52 ± 0.86	4	49.70±1.98	16	50.17 ± 0.67	13	57.78 ± 0.48
Foveal + parafoveal zone	52.75 ± 0.27	3	52.27 ± 0.67	4	45.58 ± 1.53	17	46.13 ± 0.58	16	54.61 ± 0.26
Foveal zone	25.59 ± 1.50	19	28.63 ± 1.26	10	26.78 ± 1.85	16	27.40 ± 0.71	14	31.77 ± 0.80
Parafoveal zone	55.53 ± 0.36	3	54.53 ± 0.71	4	47.23 ± 1.61	17	47.28 ± 0.66	17	56.96 ± 0.27

Note. * – percent of decreased blood flow density in the given group compared with the control group.

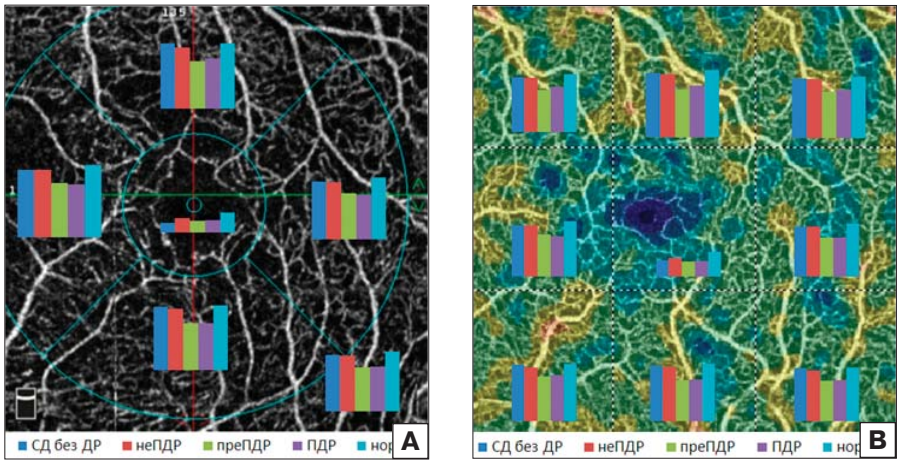

Fig. 2. Change in blood flow density in the surface vascular plexus, depending on the stage as compared to the control group. The scanning area is 3 × 3 mm. Measuring blood flow density (A) in the foveal and parafoveal zone; and (B) across 9 quadrants. The diagrams reflect the change in blood flow density in the examined zones.

Table 3. The blood flow density in the macular zone of individuals with DM and in different stages of DR (%), scanning zone 6 × 6 mm

Zones Examined	w/o DR	%*	NPDR	%*	prePDR	%*	PDR	%*	Control Group
Superior-temporal	48.73 ± 1.81	+2	46.84 ± 1.1	2	41.14 ± 1.31	14	45.71 ± 0.61	4	47.73 ± 0.64
Superior	53.15 ± 1.67	+1	51.78 ± 0.93	2	46.23 ± 1.62	12	49.47 ± 0.56	6	52.78 ± 0.64
Superior-nasal	56.43 ± 1.06	+2	54.35 ± 0.82	1	48.41 ± 1.46	12	51.54 ± 0.61	6	55.11 ± 0.42
Nasal	56.44 ± 0.98	0	54.31 ± 0.73	3	50.38 ± 1.28	10	51.74 ± 0.62	8	56.18 ± 0.61
Central	52.66 ± 0.87	0	50.83 ± 0.81	4	43.80 ± 1.38	17	45.72 ± 0.76	3	52.71 ± 0.45
Temporal	54.32 ± 0.98	0	51.12 ± 1.12	6	45.67 ± 1.54	16	47.88 ± 0.78	2	54.26 ± 0.52
Inferior-temporal	49.77 ± 2.03	1	48.03 ± 1.11	4	42.13 ± 2.53	16	44.40 ± 0.86	11	50.14 ± 0.66
Inferior	53.03 ± 1.48	0	51.08 ± 0.94	4	46.83 ± 1.70	12	47.93 ± 0.69	10	53.05 ± 0.56
Inferior-nasal	55.55 ± 1.2	+1	52.6 ± 0.76	5	48.76 ± 1.55	12	57.7 ± 0.66	8	55.21 ± 0.43
Foveal + parafoveal zone	53.35 ± 1.21	+1	51.14 ± 0.79	4	45.97 ± 1.27	13	48.40 ± 0.53	9	53.03 ± 0.45
Foveal zone	31.41 ± 1.81	9	32.16 ± 1.04	7	29.67 ± 1.22	14	30.97 ± 1.00	11	34.65 ± 1.28
Parafoveal zone	57.08 ± 0.89	+1	54.52 ± 1.01	3	47.83 ± 1.59	15	49.26 ± 0.77	12	56.26 ± 0.41

Note. * – percent of decreased blood flow density in the given group compared with the control group.

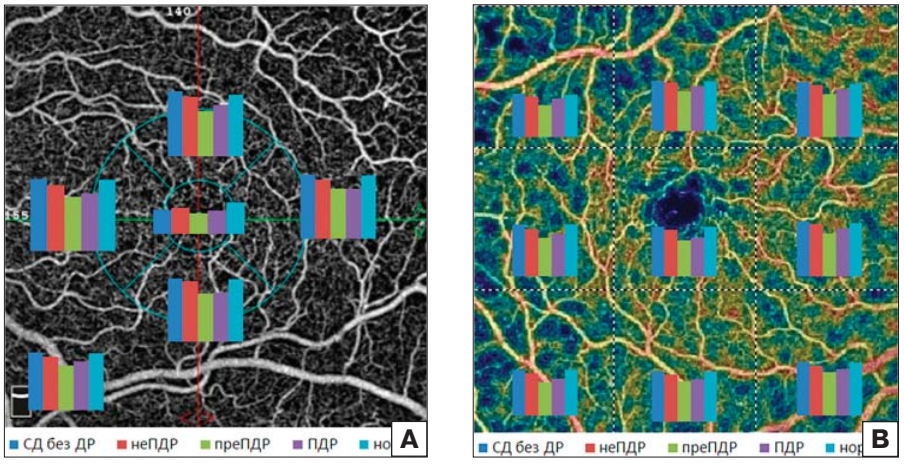

Fig. 3. Change in blood flow density in the surface vascular plexus, depending on the stage, as compared to the control group. The scanning area is 6 × 6 mm.
Measuring blood flow density (A) in the foveal and parafoveal zone; and (B) across 9 quadrants. The diagrams reflect the change in blood flow density in the examined zones.

central quadrant, as all of the blood flow density changes were quite homogenous. This was correlated with that fact that while the size of the scan increased, the changes in the FAZ on the resulting indicators turned out weaker. The differences with the control group are quite reliable ($p < 0.05$) for the groups with NPDR, with prePDR, and with PDR.

CONCLUSION

The study showed that the OCT-A method can effectively detect microvascular changes in the macular zone of patients with DM even in the earliest stages of the disease when there are no manifestations of DR on the fundus. It was found that the earliest indicator of changes in the microcirculatory channel of the retina with DM were qualitative and quantitative changes in the FAZ. These changes were evident even at preclinical stages of development of DR, and they increased with the progression of the disease. The changes could also be observed when the density of the surface vascular plexus in the capillary network decreased within the scanning fields of 3 × 3 mm. It should be noted that there was a large variability in the size of the FAZ which was observed even in the groups of healthy individuals. The individual variability of this feature obtained in the clinical analysis of the data is necessary to take into account. It is also necessary to note the impact the quality of the images obtained during scanning had on the results of the study. The quality of the pictures below 55–60 c.u. lowered the parameters of blood flow density due to the dimming of the zones corresponding to the microvascular pattern. This should be taken into account when examining patients with insufficiently transparent optical medium (cataract, hemophthalmia, endovitreal tamponade with silicone). Based on the obtained data, it can be concluded that OCT-A is a promising method for diagnosing microcirculation disorders of the retina with vascular diseases, particularly, with DR. In addition, OCT-A is a non-invasive method that does not require an intravenous dye injection, which excludes the possibility of complications and unwanted side effects. This factor confirms the advantages of using the OCT-A method for screening and monitoring of patients with DR.

References

1. *Neroev V.V., Katargina L.A., Zaitseva O.V., et al.* The state of medical assistance to patients with diabetic retinopathy in Russian Federation: results of evaluation by TADDS WHO program. Russian Ophthalmological Journal, 2016; 2: 5–10 (in Russian).
2. World Health Organization. Global Health Estimates: Deaths by Cause, Age, Sex and Country, 2000-2012. Geneva: WHO; 2014.
3. *Dedov I.I., Shestakova M.V., ed.* Federal clinical recommendations "Algorithms of specialized medical assistance to patients with diabetes mellitus". Russian Association of endocrinologists. Diabetes mellitus. Moscow; 2015 (in Russian).
4. Federal clinical recommendations "Diagnosis and treatment of diabetic retinopathy and diabetic macular edema". All-Russian public organization "Association of ophthalmologists". Available at: http://avo-portal. ru/doc/fkr 2013 (in Russian).
5. *Koskas G., Koskas F., Zurdan A.* Complex diagnostics of eye fundus pathology. Translation from French; Neroev V.V., Ryabina M.V., ed. Moscow: Prakticheskaya meditsina; 2007 (in Russian).
6. *Lumbroso B., Rispoli M.* Retinal OCT: Analysis and interpretation method. Neroev V.V., Zaytseva O.V., ed. Moscow: Aprel'; 2012 (in Russian).
7. *Lumbroso B., Huang D., Jia Y., Fujimoto J.A., Rispoli M.* Clinical guide to Angio-OCT. jJAYPEE; 2014.
8. *Zhang M., Wang J., Pechauer A.D., et al.* Advanced image processing for optical coherence tomographic angiography of macular diseases. Biomed Opt Express. 2015 Dec 1; 6(12): 4661–75.
9. *Cennamo G., Romano M.R., Nicoletti G., Velotti N., de Crecchio G.* Optical coherence tomography angiography versus fluorescein angiography in the diagnosis of ischaemic diabetic maculopathy. Acta Ophthalmol. 2016 Jul 15.
10. *Hwang T. S., Gao S.S., Liu L., et al.* Automated Quantification of Capillary Nonperfusion Using Optical Coherence Tomography Angiography in Diabetic Retinopathy. JAMA Ophthalmol. 2016 1; 134 (4 Apr.): 367–73.

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