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Ischemic maculopathy at the preproliferative stage of diabetic retinopathy: epidemiology, clinical picture and diagnosis

Tatyana R. Ogneva[1,2], Svetlana N. Tultseva[1], Fedor E. Shadrichev[1,2], Ekaterina A. Patrina[1]

[1] Academician I.P. Pavlov First St. Petersburg State Medical University, Saint Petersburg, Russia;
[2] Clinical Diagnostic Medical Center 1, Saint Petersburg, Russia

ABSTRACT

BACKGROUND: One of the leading causes of central vision loss in patients with diabetic retinopathy is ischemic maculopathy, the incidence of which in diabetic retinopathy varies depending on the stage of the disease from 20 to 77% according to fluorescein angiography results. More accurate diagnosis of ischemic maculopathy is possible using the technique of optical coherence tomography angiography (OCTA).

AIM: To study the prevalence and severity of ischemic maculopathy in patients with diabetes mellitus type 1 and 2 with preproliferative stage of diabetic retinopathy using OCTA.

MATERIALS AND METHODS: 43 patients (72 eyes) of diabetic retinopathy levels 47 and 53, according to ETDRS criterions, were included in the study. The exclusion criterion was the presence of diabetic macular edema with involvement of the center of the macula. Patients were divided into 3 groups according to the ETDRS classification of ischemic maculopathy grade. Each of them was subject to standard ophthalmologic examination, OCT with determination with determination of central retinal thickness in macula zone and OCTA to evaluate the status of the foveolar avascular zone.

RESULTS: Ischemic maculopathy level 1 was detected in 23 patients — group 1 (33 eyes), level 2 was detected in 23 patients (27 eyes) — group 2, and level 3 — in 8 patients (12 eyes) — group 3. A statistically significant difference using "IBM SPSS Statistics" version 27 was found between the foveolar avascular zone area scores of groups 1 and 2 — 0.18 mm^2 versus 0.32 mm^2 ($p < 0.001$) and between groups 1 and 3 — 0.18 mm^2 versus 0.98 mm^2 ($p < 0.001$), and between groups 2 and 3 — 0.32 mm^2 versus 0.98 mm^2 ($p < 0.008$). In group 3, negative correlations were found between best-corrected visual acuity and foveolar avascular zone circumference length ($r = –0.906$, $p = 0.02$), foveolar avascular zone ($r = –0.748$, $p = 0.033$) and circularity index ($r = –0.569$, $p = 0.141$), while no such statistically significant difference was found in the other groups.

CONCLUSIONS: In patients with diabetic retinopathy levels 47 and 53, ischemic maculopathy is revealed in 100% of cases. In 83.4% of cases, level 2 of the ischemic maculopathy is detected, and in 16.6% — level 3. Ischemic maculopathy of levels 1 and 2 has no significant effect on best-corrected visual acuity. Level 3 is clinically significant, as the change of parameters characterizing foveolar avascular zone, and first of all the increase of foveolar avascular zone circumference length above 500 μm, is associated with a decrease in best-corrected visual acuity.

Keywords: diabetic retinopathy; retinal vascular disease; diabetic macular edema; ischemic maculopathy; optical coherence tomography angiography; OCTA.

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Ишемическая макулопатия при препролиферативной стадии диабетической ретинопатии. Эпидемиология, клиника и диагностика

Т.Р. Огнева[1,2], С.Н. Тульцева[1], Ф.Е. Шадричев[1,2], Е.А. Патрина[1]

[1] Первый Санкт-Петербургский государственный медицинский университет им. акад. И.П. Павлова, Санкт-Петербург, Россия;
[2] Городской консультативно-диагностический центр № 1, Санкт-Петербург, Россия

АННОТАЦИЯ

Актуальность. Одна из ведущих причин снижения центрального зрения у пациентов с диабетической ретинопатией — ишемическая макулопатия, частота встречаемости которой при диабетической ретинопатии колеблется в зависимости от стадии заболевания от 20 до 77 % по данным флуоресцентной ангиографии. Более точная диагностика ишемической макулопатии возможна с помощью методики оптической когерентной томографии (ОКТ) с функцией ангиографии (ОКТА).

Цель — с помощью метода ОКТА изучить распространённость и выраженность ишемической макулопатии у пациентов с сахарным диабетом 1-го и 2-го типа, имеющих препролиферативную стадию диабетической ретинопатии.

Материалы и методы. В исследование включено 43 пациента (72 глаза) с диабетической ретинопатией 47-го и 53-го уровня, согласно критериям ETDRS. Критерием исключения было наличие диабетического макулярного отёка с вовлечением центра макулы. Согласно оценки уровня ишемической макулопатии по классификации ETDRS, пациенты были разделены на 3 группы. Каждому проводили стандартное офтальмологическое обследование, ОКТ с определением толщины центральной зоны сетчатки в области макулы и ОКТА с целью оценки состояния фовеолярной аваскулярной зоны.

Результаты. Уровень 1 ишемической макулопатии был выявлен у 23 пациентов — группа 1 (33 глаза), уровень 2 — у 23 пациентов (27 глаз) — группа 2, уровень 3 — у 8 пациентов (12 глаз) — группа 3. Статистически достоверная разница с использованием программы IBM SPSS Statistics 27-й версии выявлена между показателями площади фовеолярной аваскулярной зоны групп 1 и 2 — 0,18 мм^2 против 0,32 мм^2 ($p < 0,001$) и между группами 1 и 3 — 0,18 мм^2 против 0,98 мм^2 ($p < 0,001$), а также между группами 2 и 3 — 0,32 мм^2 против 0,98 мм^2 ($p < 0,008$). В группе 3 выявлены отрицательные корреляции между максимально корригированной остротой зрения и длиной окружности фовеолярной аваскулярной зоны ($r = –0,906$, $p = 0,02$), её площадью ($r = –0,748$, $p = 0,033$) и индексом циркулярности ($r = –0,569$, $p = 0,141$), в других группах такой статистически достоверной разницы не было.

Заключение. У пациентов с диабетической ретинопатией 47-го и 53-го уровня в 100 % случаев наблюдается ишемическая макулопатия. В 83,4 % случаев выявляется ишемическая макулопатия 2-го уровня и в 16,6 % — 3-го уровня. Ишемическая макулопатия 1–2-го уровня не оказывает значимого влияния на максимально корригированную остроту зрения, 3-й уровень является клинически значимым, так как изменение параметров, характеризующих фовеолярную аваскулярную зону, и в первую очередь увеличение её длины окружности выше 500 мкм, ассоциировано со снижением максимально корригированной остроты зрения.

Ключевые слова: диабетическая ретинопатия; сосудистые заболевания сетчатки; диабетический макулярный отек; ишемическая макулопатия; оптическая когерентная томография с функцией ангиографии; ОКТА.

Как цитировать

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BACKGROUND

Diabetes mellitus (DM) is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of DM is associated with damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. DM is one of the main social and economic challenges for both population and healthcare worldwide. The estimated DM prevalence is 9%, the disease and its complications cause approximately 1.5 million deaths per year [1]. By 2030, DM is predicted to become the 7th leading cause of death worldwide [2]. Registry data as of February 2, 2025, show that DM was diagnosed in a total of 5,482,678 patients in 84 regions of Russia. In 2024, the prevalence of type 1 and type 2 DM in Russia averaged 194.2 and 3211.1 per 100,000 population,* respectively.

The main DM complications are microvascular changes which increase the risk of stroke, infarction, and lower-extremity venous thromboembolism [3]. A classic marker of the diabetic microangiopathy severity is diabetic retinopathy (DR) [4]. The World Health Organization staging states that damage to the retinal capillaries is the leading diabetic retinal change [5]. Capillary occlusion induces the rest DR development mechanism, resulting in vasoproliferative changes and permanent visual function loss. The visual function prognosis depends on several characteristics of capillary non-perfusion, such as location, initial area, and area increase rate [6, 7]. Currently, there are the following four types of capillary non-perfusion associated with DR: peripheral, mid-peripheral, central, and generalized. The rate of non-perfused area increase has been demonstrated to be the highest in peripheral ischemia, followed by the mid-peripheral, central, and generalized in ascending order.

When ischemia is located at the mid-periphery and central fundus, the risk of progression to a generalized form is the highest. Therefore, detection of macular and perifoveal ischemia in early DR may be a marker of the DR severity, which has high clinical value [8].

The pathogenesis of retinal capillary occlusion is under study. Hyperglycemia is considered to increase retinal glucose levels, thereby slightly increasing vascular endothelial growth factor (VEGF), then expression of intercellular adhesion molecules, primarily ICAM1 [9]. This leads to "a permissive effect," creating a vicious circle. Increased ICAM1 levels accelerates the binding rate of activated leukocytes to capillary endothelial cells, which often leads to endotheliocyte death. Endothelial cell loss over time depletes the replicative capacity of the endothelium and results in capillary occlusion. Foci of tissue hypoxia are formed in this area, which induce further increased VEGF expression.

The association of accidental occlusion of one retinal capillary with an increase in the non-perfusion area is quite significant. The process continues until it reaches a high oxygenation site, usually adjacent to a large retinal arteriole or venule [10].

The most informative methods for diagnosing retinal ischemia are fundus fluorescein angiography (FA) and optical coherence tomography angiography (OCTA). Widefield or multifield FA not only detects, but also measures peripheral non-perfusion area. The diagnosis of macular ischemia has some challenges. Firstly, FA cannot assess individual capillary plexuses, so early macular ischemia may be missed. Secondly, significant hyperfluorescence associated with rapid dye leakage challenges the assessment of the non-perfusion area margins and integrety of the parafoveal capillary ring. However, there are 8 grades of macular ischemia (MI) identified using FA according to Early Treatment of Diabetic Retinopathy Study (ETDRS) report. The grading is based on the following three main criteria: the severity of perifoveal capillary loss, increase in perimeter length of the foveal avascular zone (FAZ), and foveal capillary ring integrity [11].

Currently, the criteria for evaluating MI using OCTA are under study. This method is considered to have several advantages in assessing capillary perfusion in the posterior pole. The main one is that it analyzes each capillary plexus individually and objectively assesses both perfusion and vascular density. The parameters characterizing FAZ, such as area, perimeter length, and circularity, provide accurate understanding of the macular perfusion status. Like FA, OCTA has its disadvantages. They include artifacts associated with microsaccades and decentration, as well as so-called shadow artifacts leading to incorrect data evaluation. Therefore, for studies, manual correction of the results is required to eliminate corrupted data [12]. Nevertheless, OCTA is currently considered to be more accurate in diagnosing MI than FA [13]. Moreover, associations were found between OCTA characteristics of the FAZ and perifoveal area with the severity of visual acuity decrease in patients with DR [14], presence of peripheral ischemic areas [15], and significance of these parameters in choosing the treatment strategy for these patients. Thus, studies of the effect of anti-VEGF and anti-inflammatory drugs on MI, including those targeted at Ang2, demonstrate promising results, transforming uncontrolled MI into "a new therapeutic target" [16].

Notably, there are currently few studies of the MI Incidence at different DR stages, clinical significance, and its progression rate using OCTA. Available publications

* "Endocrinology Research Center" State-Funded Research Facility of the Ministry of Health of the Russian Federation. Database of clinical and epidemiological monitoring of diabetes mellitus in the Russian Federation. Web-site: https://sd.diaregistry.ru/#content (Accessed: February 2, 2025).

are mainly based on FA data, which suggests only approximate values. This data shows that the incidence of MI associated with DR varies with the disease stage from 20% to 77%. MI is most often detected at the pre-proliferative (59.7%) and proliferative stages (77.2%) [17].

The lack of consensus on the diagnosis and treatment of MI associated with DR and the lack of objective methods for assessing the condition demonstrate the relevance of studies of its incidence and the main risk factors for progression [18].

The study aimed to use OCTA to assess the MI prevalence and severity in patients with type 1 and 2 DM with pre-proliferative DR.

METHODS

A total of 43 patients (72 eyes) with mean age of 56.2 (25–79) years old were examined and enrolled, including 20 men (34 eyes) and 23 women (38 eye), with type 1 and 2 DM and pre-proliferative diabetic retinopathy at the Regional Endocrinology Center of the City Consultative and Diagnostic Center No. 1 and the Ophthalmology Department with Astakhov clinic of Pavlov First Saint Petersburg State Medical University.

Inclusion criteria were type 1 or 2 DM, age over 18 years, pre-proliferative diabetic retinopathy (PPDR) with at least one of the following three signs: moderate intra-retinal microvascular abnormalities at least in one quadrant, venous abnormalities in two or more quadrants, and multiple retinal hemorrhages in four quadrants [19]. All enrolled patients had levels 47 and 53 DR according to the ETDRS classification [11] and refractive spherical equivalent below 5 D and signed the informed consent form.

Non-inclusion criteria were diabetic macular edema involving the center of the macula in the study eye; cataract or other eye diseases which may affect fundus examination or OCT/OCTA signal; other retinal vascular diseases or any eye diseases which may affect the retinopathy status; any eye surgery, including laser one; intravitreal therapy within 6 months; and HbA1c >12% before the study.

Ass per the inclusion criteria, both eyes of one patient could be included in the study.

The ophthalmological examination included a measurement of best corrected visual acuity (BCVA). Structural OCT with an assessment of central retinal thickness was performed in all patients to identify clinically significant macular edema (non-inclusion criterion).

Macular and peripapillary OCTA of 3 × 3 and 6 × 6 mm^2 areas was performed using Cirrus Zeiss 5000 AngioPlex (Zeiss) SD-OCTA to assess capillary perfusion density, vessel density in the superficial capillary plexus, and FAZ status, including foveal capillary ring integrity, FAZ perimeter length, area, and circularity. All OCTA images were additionally assessed for quality. The measurement quality criteria were well-focused capillary networks with no cropped images, duplicated vessels, or artifacts. In case of decentration and when automatic assessment of FAZ could not be performed, the images were processed manually.

Multimodal FA (HRA Spectralis Cirrus photo 800) was performed in a group of patients scheduled to have panretinal photocoagulation in the peripheral capillary nonperfusion area.

Additionally, glycated hemoglobin (HbA1c) was assessed.

Statistical data analysis was performed using IBM SPSS Statistics, version 27. The study groups were homogeneous, which was confirmed by the Kruskal–Wallis test. The significance of differences between unrelated samples of patients with MI of different grades was assessed using the nonparametric Mann–Whitney *U* test. Correlations between both within the groups and all values were assessed using the Pearson correlation coefficient. Quantitative parameters are shown as median, minimum, and maximum values (min–max).

To assess the MI severity, ETDRS classification (Grading of diabetic macular ischemia according to ETDRS Report No. 11) was used [11]. As the MI assessment criteria are similar, this classification has been adapted and is also used for OCTA in some cases [20]. However, the “capillary loss” parameter was replaced with “vessel density” and “perfusion density”, the remaining characteristics were unchanged.

According to the classification of MI associated with DR, all enrolled patients were divided into the following groups: group 1 = grade 1, 2 MI areas; group 2 = grade 2; group 3 = grade 3 or higher.

RESULTS

The study revealed that in all examined patients, capillary perfusion density in the macula was 17.8% (3.8–29.3), macular vessel density in the superficial capillary plexus (SCP) was 9.7% (2.5–18.5), FAZ area was 0.36 mm^2 (0.05–2.1), FAZ perimeter length was 2.59 mm (0.19–7.14), FAZ circularity was 0.58 (0.31–0.82), and BCVA was 0.69 (0.1–1.0). The HbA1c level was 8.3% (5.3–11.2). Grade 1 MI was identified in 23 patients (33 eyes) in group 1, grade 2 MI was reported in 23 patients (27 eyes) in group 2 (Fig. 1), and 8 patients (12 eyes) in group 3 had grade 3 MI (Fig. 2).

In group 1, macular SCP vessel density was 11.1% (2.6–17.5), macular capillary perfusion density in the SCP was 20.9% (5.8–29.3), FAZ area was 0.18 mm^2 (0.05–0.28), FAZ perimeter length was 1.96 mm (0.82–2.72), FAZ circularity was 0.59 (0.32–0.76), and BCVA was 0.64 (0.1–1.0). In group 2, macular SCP vessel density was

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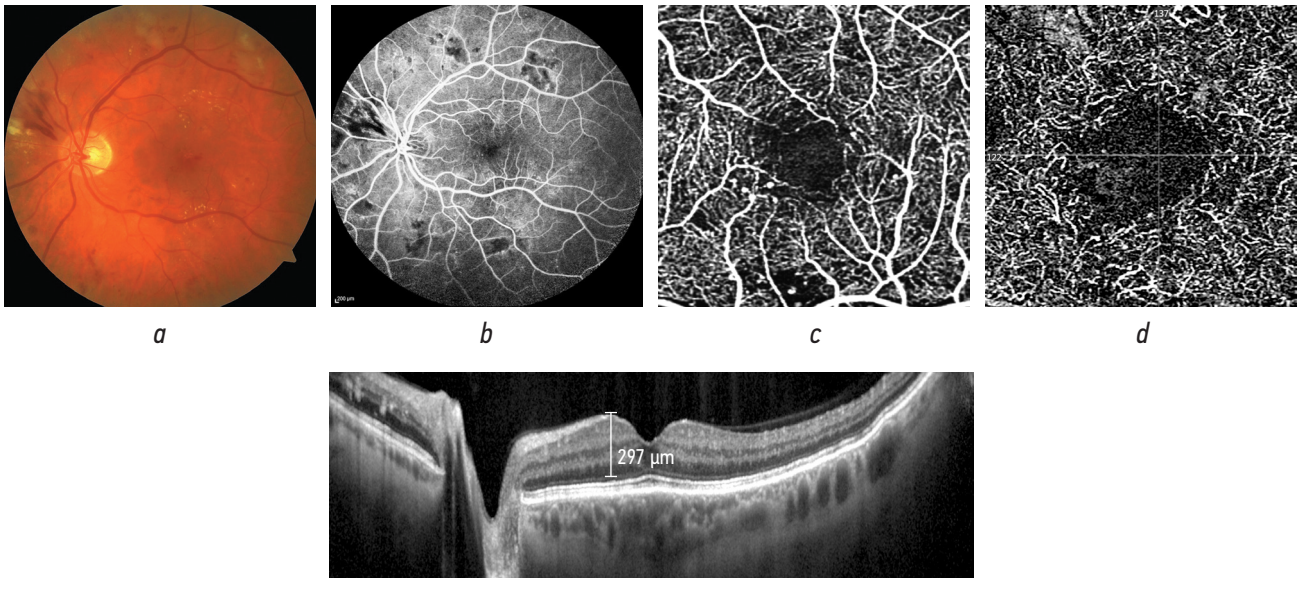
8.64% (2.9–12.7), capillary perfusion density was 15.9% (5.2–24.2), FAZ area was 0.32 mm^2 (0.29–0.52), FAZ perimeter length was 2.63 mm (2.13–3.19), FAZ circularity was 0.56 (0.38–0.77), and BCVA was 0.7 (0.1–1.0). In group 3, macular SCP vessel density was 8.4% (2.5–18.5), capillary perfusion density was 14.3% (3.8–25.2), FAZ area was 0.98 mm^2 (0.59–2.1), FAZ perimeter length was 5.74 mm (5.1–7.14), FAZ circularity was 0.56 (0.45–0.64), and BCVA was 0.543 (0.3–0.5).

A statistically significant difference was found in macular SCP perfusion density between groups 1 and 2 (20.9% vs. 15.9%, respectively; $p < 0.001$) and groups 1 and 3 (20.9% vs. 14.3%, respectively; $p = 0.023$; Fig. 3). A difference in SCP vessel density was significant between groups 1 and 2 (11.1% vs. 8.64%, respectively; $p = 0.004$) and not significant between groups 1 and 3 (11.1% vs. 8.4%; $p = 0.158$) and groups 2 and 3 (8.64% vs. 8.4%; $p = 1.0$; Fig. 4). A significant difference in FAZ area was noted between groups 1 and 2 (0.18 mm^2 vs. 0.32 mm^2; $p < 0.001$), groups 1 and 3 (0.18 mm^2 vs. 0.98 mm^2; $p < 0.001$), and groups 2 and 3 (0.32 mm^2 vs. 0.98 mm^2; $p < 0.008$). A significant difference in FAZ perimeter length was reported between groups 1 and 2 (1.96 mm vs. 2.63 mm; $p < 0.001$), groups 1 and 3 (1.96 mm vs. 5.74 mm; $p < 0.001$), and groups 2 and 3 (2.63 mm vs. 5.74 mm; $p = 0.008$).

In group 1, a statistically significant positive correlation was found between FAZ area and SCP vessel density ($r = 0.487$, $p = 0.006$). Positive correlations were also detected between BCVA and FAZ perimeter length ($r = 0.209$, $p = 0.296$) and between BCVA and FAZ circularity ($r = 0.115$, $p = 0.567$), but both associations were not statistically significant.

In group 2, statistically significant positive correlations were noted between BCVA and capillary perfusion density ($r = 0.675$, $p < 0.001$) and SCP vessel density ($r = 0.654$, $p < 0.001$). Correlations between BCVA and FAZ area ($r = –0.196$, $p = 0.359$) and between BCVA and FAZ perimeter length ($r = 0.134$, $p = 0.635$) were not statistically significant. Correlation between BCVA and FAZ circularity ($r = 0.364$, $p = 0.182$) also did not reach statistical significance.

In group 3, there were no significant correlations between BCVA and SCP vessel density ($r = –0.559$, $p = 0.149$) and between BCVA and capillary perfusion density ($r = –0.361$, $p = 0.38$). All FAZ parameters were found to be interdependent. Statistically significant strong positive correlation was detected between FAZ area and



a *b* *c* *d* *e*

Fig. 1. Patient, 62 years old, diabetes mellitus type 2, left eye preproliferative stage of diabetic retinopathy, level 2 ischemic maculopathy: *a*, fundus photography; *b*, fluorescein angiography data; *c*, OCTA data 3×3 mm^2, superficial capillary plexus (perfusion density 12.9%, foveolar avascular zone area 0.68 mm^2, foveolar avascular zone circumference length 3.73 mm, circularity index 0.42; *d*, OCTA data 3×3 mm^2, deep capillary plexus; *e*, fundus OCT data, retinal thickness in the macular area 297 µm, best corrected visual acuity 0,9

Рис. 1. Пациентка, 62 года, сахарный диабет 2-го типа, левый глаз, препролиферативная стадия диабетической ретинопатии, ишемическая макулопатия 2-го уровня: *a* — фотография глазного дна; *b* — данные флуоресцентной ангиографии; *c* — данные оптической когерентной томографии-ангиографии 3×3 мм^2, поверхностное капиллярное сплетение (плотность перфузии 12,9 %, площадь фовеолярной аваскулярной зоны 0,68 мм^2, длина её окружности 3,73 мм, показатель индекса циркулярности 0,42; *d* — данные оптической когерентной томографии-ангиографии 3×3 мм^2, глубокое капиллярное сплетение; *e* — данные оптической когерентной томографии глазного дна, толщина сетчатки в макулярной зоне 297 мкм, максимальная корригированная острота зрения 0,9

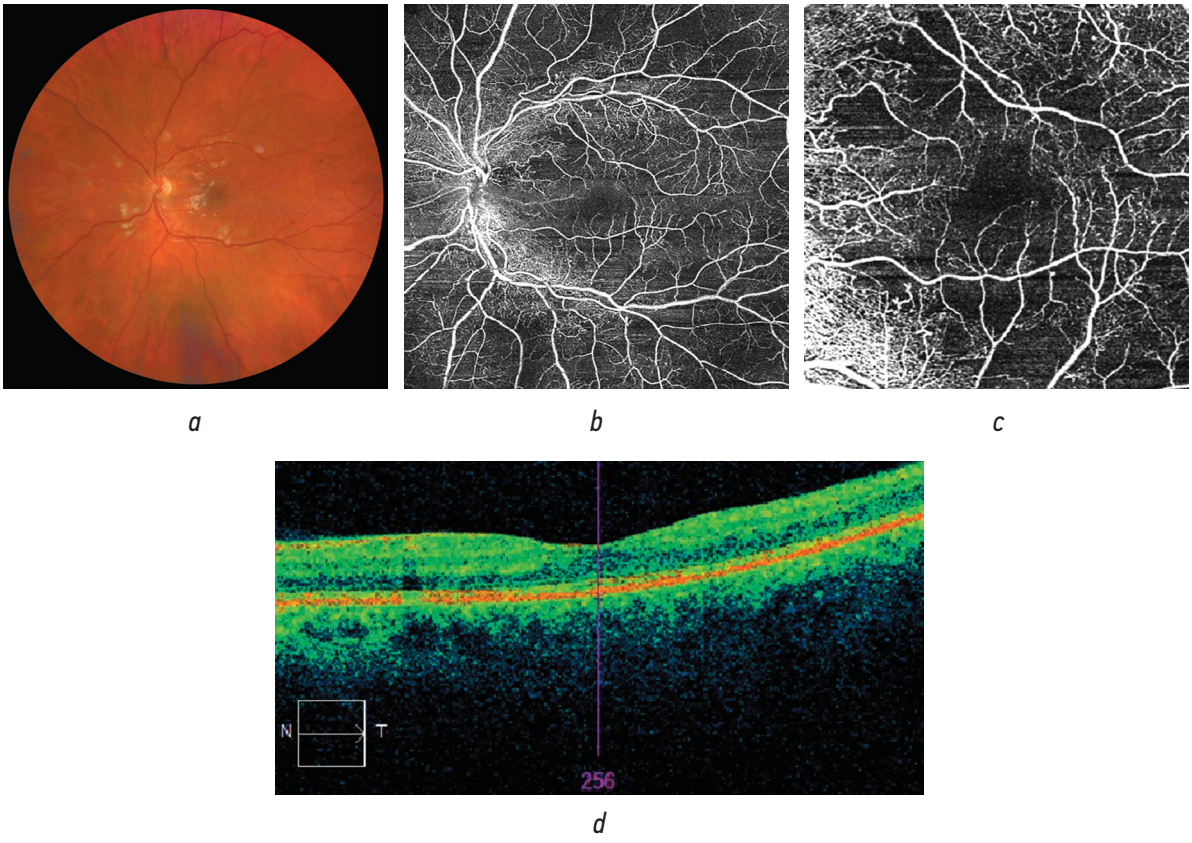


Fig. 2. Patient, 25 years old, diabetes mellitus type 1, left eye preproliferative stage of diabetic retinopathy (level 47), level 3 ischemic maculopathy: *a*, fundus photography; *b*, OCTA data 8×8 mm^2; c, OCTA data 6×6 mm^2, superficial capillary plexus (perfusion density 7.3%, foveolar avascular zone area 1.97 mm^2, foveolar avascular zone circumference length 6.49 mm, circularity index 0.59; *d*, OCT data of macular zone, retinal thickness in the macular area 236 μm, best corrected visual acuity 0.5

Рис. 2. Пациентка, 25 лет, сахарный диабет 1-го типа, левый глаз, препролиферативная стадия диабетической ретинопатии (47-й уровень), ишемическая макулопатия 3-го уровня: *a* — фотография глазного дна; *b* — данные оптической когерентной томографии-ангиографии 8×8 мм^2; *c* — данные оптической когерентной томографии-ангиографии 6×6 мм^2, поверхностное капиллярное сплетение (плотность перфузии 7,3 %, площадь фовеолярной аваскулярной зоны 1,97 мм^2, длина окружности фовеолярной аваскулярной зоны 6,49 мм, показатель индекса циркулярности 0,59; *d* — данные оптической когерентной томографии макулярной зоны, толщина сетчатки в макулярной зоне 256 мкм, максимальная корригированная острота зрения 0,5

FAZ perimeter length (r = 0.940, p < 0.001), and strong correlation was noted between FAZ circularity and FAZ perimeter length (r = 0.840, p = 0.009). However, negative correlations were found between BCVA and FAZ perimeter length (r = –0.906, p = 0.02), BCVA and FAZ area (r = –0.748, p = 0.033), and between BCVA and FAZ circularity (r = –0.569, p = 0.141).

DISCUSSION

Previously published data showed that the MI incidence in patients with pre-proliferative DR was 59.7% [17], which significantly differs from our results indicating MI in 100% of cases. The most likely reason for this difference is the method to diagnose MI. No dye leakage on OCTA images reliably indicates early MI manifestations corresponding to grade 1–2. This assumption is supported by the fact that OCTA detected grade 1–2 MI was in the vast majority of cases (83.4% of patients), and only 16.6% of patients with pre-proliferative DR had grade 3 MI.

It is difficult to compare the FAZ parameters obtained in patients with levels 47 and 53 DR according to the ETDRS classification with data from non-Russian studies, as patients with levels 43, 47, and 53 are most often pooled into one observation group. Therefore, there are significant differences in our study, with a tendency to higher values.

Thus, in RICHARD including 60 patients with DR (levels 43, 47, 53) and completed in 2024, mean FAZ area was 0.28 ± 0.11 mm^2, FAZ perimeter length was 2.21 ± 0.5 mm, and FAZ circularity was 0.7 ± 0.07, which are significantly lower than the above results. Dividing patients with levels 47 and 53 into separate groups changed these

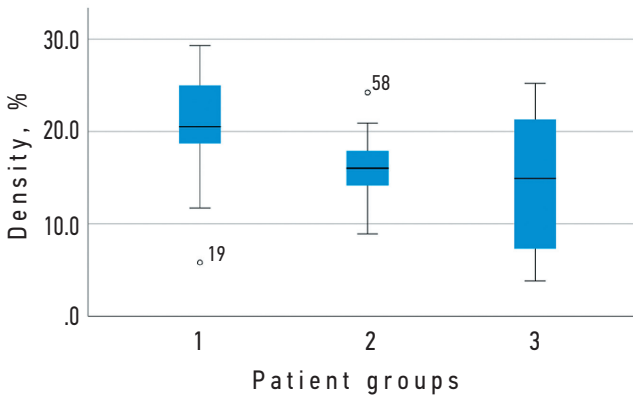


Fig. 3. Distribution graph of perfusion density index in the superficial capillary plexus of the macular area in patients with different levels of ischemic maculopathy. Statistical difference was obtained between groups 1 and 2 ($p < 0.001$), and groups 1 and 3 ($p = 0.023$)

Рис. 3. График распределения показателя плотности перфузии в поверхностном капиллярном сплетении макулярной зоны пациентов с разным уровнем ишемической макулопатии. Статистическая разница получена между группой 1 и 2 ($p < 0{,}001$) и группой 1 и 3 ($p = 0{,}023$)

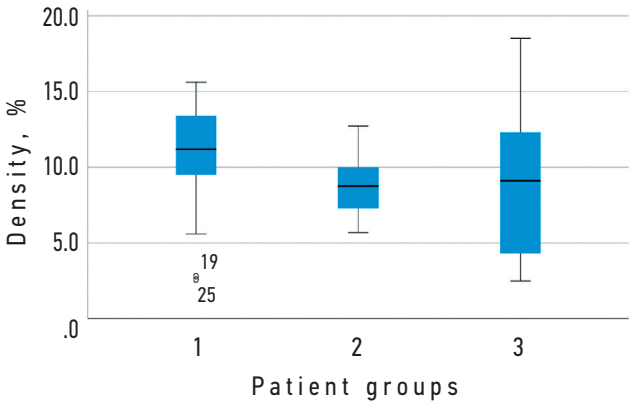


Fig. 4. Distribution graph of the vascular density index in the superficial capillary plexus of the macular area in patients with different levels of ischemic maculopathy. Statistical difference was obtained between groups 1 and 2 ($p = 0.004$). Between groups 1 and 3, the difference is not significant ($p = 0.158$)

Рис. 4. График распределения показателя плотности сосудов в поверхностном капиллярном сплетении макулярной зоны пациентов с разным уровнем ишемической макулопатии. Статистическая разница получена между группой 1 и 2 ($p = 0{,}004$). Между группой 1 и 3 разница недостоверная ($p = 0{,}158$)

parameters to 0.31 ± 0.14, 0.25 ± 0.13, and 2.36 ± 0.67 mm^2 for level 47 and to 2.09 ± 0.62, 0.69 ± 0.1, and 0.68 ± 0.11 mm^2 for level 52, respectively, which made them almost similar to the presented data [14].

Importantly, BCVA remains quite high and averages 0.69 at the pre-proliferative DR stage, whereas it is 0.54 in patients with grade 3 MI. The revealed significant correlations between BCVA, vessel density, and macular SCP perfusion density in patients with grade 2 MI and no clear association with the FAZ parameters indicate that grade 1–2 MI is clinically insignificant, and a decrease in vessel and perifoveal perfusion density demonstrates an increasing risk of MI area enlargement, which may later affect BCVA. In contrast, in patients with grade 3 MI, significant relationship of BCVA with perfusion and macular SCP vessel density is not observed, but strong negative correlations with all FAZ parameters are revealed, which clearly indicates the MI clinical significance. That is, FAZ perimeter length exceeding 5.0 mm in combination with compromised integrity of the perifoveal capillary ring by more than a half can be considered OCTA markers of clinically significant MI.

It is highly important to detect macular hypoperfusion in pre-proliferative DR; however, one should remember that according to several authors, these changes are followed by a hyperperfusion phase associated with intraretinal microvascular abnormalities and microaneurysms [5]. Parafoveal microaneurysms are considered to be a sign of MI development and progression, as well as structural disorders of the capillary and precapillary walls.

Follow-up macular OCTA in patients with pre-proliferative DR (especially with levels 47 and 53 corresponding to the moderate and severe stages of non-proliferative DR according to ETDRS) may demonstrate the need for panretinal photocoagulation in the peripheral nonperfusion area or intravitreal angiogenesis inhibitors to stabilize the capillary and precapillary walls. These procedures will be effective in preventing MI progression in patients with DR.

CONCLUSION

All patients with levels 47 and 53 DR had MI. Grade 2 and 3 MI was detected in 83.4% and 16.6% of cases, respectively.

Grade 1–2 MI did not significantly affect BCVA.

Grade 3 MI was clinically significant, as a change in the FAZ parameters, primarily an increase in FAZ perimeter length above 5.0 mm, was associated with BCVA worsening.

Modern diagnostic methods, in particular OCT and OCTA, allow controlling progression of hypoperfusion associated with capillary occlusion or intraretinal microvascular abnormalities and microaneurysms, indicating the increasing severity of MI and DR in general.

ADDITIONAL INFO

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final

approval of the version to be published and agree to be accountable for all aspects of the study. Personal contribution of each author: T.R. Ogneva, substantial contribution to the concept and design of the paper, collection, analysis and processing of material, statistical processing of data, writing, editing; S.N. Tultseva, substantial contribution to the conception and design of the work, editing, final approval of the version to be published writing of the text; F.E. Shadrichev, substantial contribution to the conception and design of the work, writing, editing; E.A. Patrina, collection, analysis and processing of material.

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Ethical Committee. The study protocol was approved by the local ethical committee of the Academician I.P. Pavlov First St. Petersburg State Medical University (No. 4 dated 2023 Oct. 23).

Consent for publication. Written consent was obtained from the patients for publication of relevant medical information and all of accompanying images within the manuscript.

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Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией. Личный вклад каждого автора: Т.Р. Огнева — существенный вклад в концепцию и дизайн работы, сбор, анализ и обработка материала, статистическая обработка данных, написание текста, редактирование; С.Н. Тульцева — существенный вклад в концепцию и дизайн работы, редактирование, окончательное утверждение версии, подлежащей публикации, написание текста; Ф.Е. Шадричев — существенный вклад в концепцию и дизайн работы, написание текста, редактирование; Е.А. Патрина — сбор, анализ и обработка материала.

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AUTHORS' INFO

***Tatyana R. Ogneva,** MD; address; 6–8 Lva Tolstogo st., Saint Petersburg, 197022, Russia; ORCID: 0000-0003-4533-7590; e-mail: exclamation@bk.ru

ОБ АВТОРАХ

***Татьяна Романовна Огнева;** адрес: Россия, 197022, Санкт-Петербург, ул. Льва Толстого, д. 6–8; ORCID: 0000-0003-4533-7590; e-mail: exclamation@bk.ru

* Corresponding author / Автор, ответственный за переписку

AUTHORS' INFO

Svetlana N. Tultseva, MD, Dr. Sci. (Medicine);
ORCID: 0000-0002-9423-6772; eLibrary SPIN: 3911-0704;
e-mail: tultceva@yandex.ru

Fedor E. Shadrichev, MD, Cand. Sci. (Medicine);
ORCID: 0000-0002-7790-9242; e-mail: shadrichev_dr@mail.ru

Ekaterina A. Patrina; ORCID: 0009-0001-8736-3677;
email: katunya_pat@mail.ru

ОБ АВТОРАХ

Светлана Николаевна Тульцева, д-р мед. наук;
ORCID: 0000-0002-9423-6772; eLibrary SPIN: 3911-0704;
e-mail: tultceva@yandex.ru

Фёдор Евгеньевич Шадричев, канд. мед. наук;
ORCID: 0000-0002-7790-9242; e-mail: shadrichev_dr@mail.ru

Екатерина Андреевна Патрина; ORCID: 0009-0001-8736-3677;
e-mail: katunya_pat@mail.ru

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