

PERSONALIZED ANALYSIS OF FOVEAL AVASCULAR ZONE WITH OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY

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✧ **Aim.** To investigate the relationship between the foveal avascular zone (FAZ) and inner nuclear layer (INL)-free zone in order to provide a personalized approach for evaluation of the FAZ area with optical coherence tomography-angiography (OCTA). **Material and methods.** Thirty-six healthy individuals (36 eyes) and 9 patients (12 eyes) with nonproliferative diabetic retinopathy (nPDR) were included in this study. The FAZ area as well as INL-free zone were measured in superficial capillary plexus on OCTA images. The FAZ area, INL-free area, and the ratio of the INL-free area to the FAZ area were compared between healthy subjects and nPDR patients. **Results.** The mean FAZ area in healthy subjects and nPDR patients was 0.33 ± 0.1 and 0.56 ± 0.28 mm² ($p < 0.05$), respectively. The mean INL-free zone in healthy subjects and nPDR patients was 0.33 ± 0.07 and 0.28 ± 0.1 mm² ($p > 0.05$), respectively. The ratio of the INL-free area to the FAZ area in healthy subjects and nPDR patients was 1.08 ± 0.25 and 0.57 ± 0.2 ($p < 0.001$), respectively. Receiver operating characteristic analysis showed that the ratio of the INL-free area to the FAZ area had the higher area under curve (0.98; 91.7% sensitivity and 97.2% specificity) compared to the FAZ area (0.8; 66.7% sensitivity and 87.1% specificity) for differentiating nPDR from healthy eyes. **Conclusion.** This study showed that personalized analysis of the FAZ area based on the relationship between the actual FAZ and INL-free zone has better diagnostic accuracy compared to the conventional FAZ area measurement on OCTA images.

✧ **Keywords:** optical coherence tomography-angiography; foveal avascular zone; diabetic retinopathy.

ПЕРСОНАЛИЗИРОВАННЫЙ АНАЛИЗ ФОВЕАЛЬНОЙ АВАСКУЛЯРНОЙ ЗОНЫ С ПОМОЩЬЮ ОПТИЧЕСКОЙ КОГЕРЕНТНОЙ ТОМОГРАФИИ-АНГИОГРАФИИ

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✧ **Цель** — разработать высокочувствительный метод оценки изменений площади фовеальной аваскулярной зоны (ФАЗ) с помощью оптической когерентной томографии-ангиографии (ОКТА), основанный на соотношении ФАЗ и зоны отсутствия внутреннего ядерного слоя (ВЯС). **Материал и методы.** В исследование включили 36 здоровых добровольцев (36 глаз) и 9 пациентов (12 глаз) с неproлиферативной диабетической ретинопатией (нПДР). Всем пациентам была выполнена ОКТА. Площадь зоны отсутствия ВЯС и площадь ФАЗ, а также их отношение были определены на изображениях поверхностного капиллярного сплетения и сопоставлены между здоровыми добровольцами и пациентами с нПДР. **Результаты.** Среднее значение площади ФАЗ у здоровых добровольцев и пациентов с нПДР составило $0,3 \pm 0,1$ и $0,56 \pm 0,28$ мм² ($p < 0,05$) соответственно; среднее значение площади зоны отсутствия ВЯС у здоровых добровольцев и пациентов с нПДР — $0,33 \pm 0,07$ и $0,28 \pm 0,1$ мм² ($p > 0,05$) соответственно; отношение площади зоны отсутствия ВЯС и площади ФАЗ у здоровых добровольцев

и пациентов с нПДР составило $1,08 \pm 0,25$ и $0,57 \pm 0,2$ ($p < 0,001$) соответственно. При ROC-анализе соотношение площади зоны отсутствия ВЯС и площади ФАЗ имело большую площадь под кривой (0,98; чувствительность 91,7 % и специфичность 97,2 %) по сравнению с площадью ФАЗ (0,8; чувствительность 66,7 % и специфичность 87,1 %) при использовании данных диагностических критериев для дифференцировки пациентов с нПДР и здоровых пациентов. **Заключение.** Данное исследование показало, что анализ ФАЗ, основанный на оценке соотношения площади зоны отсутствия ВЯС и площади ФАЗ на изображениях ОКТА, обладает большей диагностической ценностью и точностью в диагностике нПДР по сравнению с традиционной оценкой площади ФАЗ.

✧ **Ключевые слова:** оптическая когерентная томография-ангиография; фовеальная аваскулярная зона; диабетическая ретинопатия.

Optical coherence tomography angiography (OCTA) is a new non-invasive technique that allows visualization of blood vessels in the posterior segment of the eye with a resolution of up to 20 μm . One of the most important clinical applications of OCTA is the analysis of the macular area microvasculature. OCTA confirms the complex microvasculature of the retina in the macular region, which includes superficial and deep vascular plexuses [6, 12]. Each plexus has an independent functional significance; hence, their separate analysis provides additional information on the pathophysiology of vascular retinal diseases [1]. In addition to visualization, OCTA provides quantitative data on the status of the microvasculature. The most practically important indicators are the density of superficial and deep vascular plexuses as well as shape and area of the foveal avascular zone (FAZ) [6, 9].

The morphometric analysis beginning with the estimation of the FAZ area is most often used to determine severity and dynamics of retinopathies of vascular nature. Although an increase in FAZ area is noted in diabetic retinopathy (DR), as well as in branch or central vein occlusions, a substantial increase of this index (up to 10-fold) from the normal value is a significant obstacle to the practical application of FAZ area as a routine diagnostic criterion [8]. Thus, while assessing the FAZ area in an individual patient, it is not always possible to decide unambiguously whether the index is normal or pathologically increased. Consequently, the development of a method for personalized estimation of the FAZ area, considering the individual normal value, is of highest interest. This could be achieved by studying the relationship of FAZ with histological structures in the foveal region, as they are more resistant to ischemic injury than the microvasculature.

Recently, Park et al. (2016) used a specific segmentation algorithm to characterize the middle capillary plexus (referring to the deep capillary plexus in standard segmentation), which lies in the inner boundary of the internal nuclear layer (INL) and includes terminal segments of capillaries forming the FAZ [10]. Thus, the middle capillary plexus has a close anatomical relationship with the INL and hence, the INL-free zone in the center of the macula has to correspond to the FAZ area.

Considering the above mentioned facts, the objective of the present research was to develop a sensitive method for estimating changes in the FAZ based on its relationship with the INL-free zone.

MATERIALS AND METHODS

Study population

This study included healthy volunteers and patients with mild to moderate non-proliferative DR.

Inclusion criteria for patients with DR were age from 18 through 60 years, absence of macular edema according to OCT, and OCT signal intensity $\geq 7/10$. For the analysis, only OCTA images without artifacts in the projection of the FAZ were used.

Exclusion criteria included myopia >3.0 D; hypermetropia >2.0 D; proliferative DR; absence of DR signs; reduced transparency of the optical media, including cataracts of severity $>$ degree 1, according to the Lens Opacity Classification System scale III; changes in the vitreoretinal interface, such as fibrosis of the internal limiting membrane, vitreomacular adhesion, vitreomacular traction syndrome, and macular hole; macular edema; and subfoveal detachment of the neuroepithelium. Macular edema was defined as intraretinal fluid accumulation in the projection of the central subfield.

Optical coherence tomography

After a standard ophthalmological examination, all patients underwent OCTA on the Copernicus REVO Spectral Optical Coherent Tomograph (Optopol, Poland) using the Retinal Angiography protocol in the 3×3 -mm zone (2 sets, each consisting of 200 B-scans and 320 A-scans). The FAZ area was determined on the image of the superficial capillary plexus using the ImageJ program after scaling the image.

Definition of the INL absence zone

The INL-free zone was visualized using automatic segmentation lines with Copernicus REVO software. A special feature of this tomography software is the formation of an “absence zone of the OCT” signal on the full-face image if the external and internal lines of the segmentation intersect (Fig. 1). In order to visualize the INL-free zone, segmentation lines passing along the border

of the internal plexiform layer (IPL)/INL and the internal limiting membrane (ILM) were used. The ILM segmentation line was shifted in the direction of the IPL/INL line to a fixed depth.

The development of a method for estimating the area of the INL-free zone included three stages:

1. Determination of the INL depth along the edge of the INL-free zone to estimate the magnitude of the segmentation line displacement along the ILM boundary.
2. Testing the correspondence between the area of the INL-free zone and the FAZ area for various parameters related to the displacement of the ILM segmentation lines within the average statistical depth of the INL boundary.
3. Ascertaining the relationship between the FAZ area and the area of the INL-free zone in healthy volunteers and in DR patients.

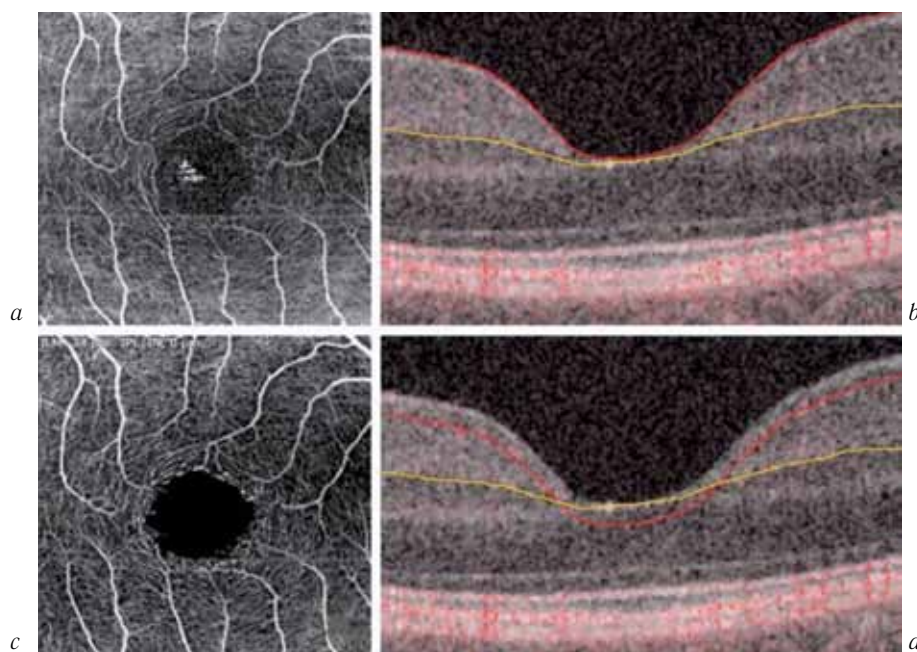


Fig. 1. A representative example of visualization of foveal avascular zone (FAZ) and inner nuclear layer (INL)-free area with optical coherence tomography angiography; *a* — FAZ is visible on the superficial capillary plexus slab; *b* — automatic segmentation lines delineating the inner limiting membrane (ILM) and the border between the inner plexiform layer (IPL)/INL set without shift (ILM = 0 μ m, IPL/INL = 0 μ m); *c* — INL-free zone is clearly visible on the image of the superficial capillary plexus slab; *d* — automatic segmentation line delineating ILM shifted toward INL in order to show INL-free zone (ILM = -34 μ m, IPL/INL = 0 μ m)

Рис. 1. Пример визуализации фовеальной аваскулярной зоны (ФАЗ) и зоны отсутствия внутреннего ядерного слоя (ВЯС): *a* — визуализация ФАЗ на изображении поверхностного капиллярного сплетения; *b* — на соответствующем В-скане линии автоматической сегментации внутренней пограничной мембраны (ВПМ) и внутреннего плексиформного слоя (ВПС)/ВЯС для визуализации поверхностного капиллярного сплетения расположены без смещения (ВПМ = 0 мкм, ВПС/ВЯС = 0 мкм); *c* — визуализация зоны отсутствия ВЯС на изображении поверхностного капиллярного сплетения; *d* — на соответствующем В-скане линия автоматической сегментации ВПМ смещена в направлении линии автоматической сегментации ВЯС для визуализации зоны отсутствия ВЯС (ВПМ = -34 мкм, ВПС/ВЯС = 0 мкм)

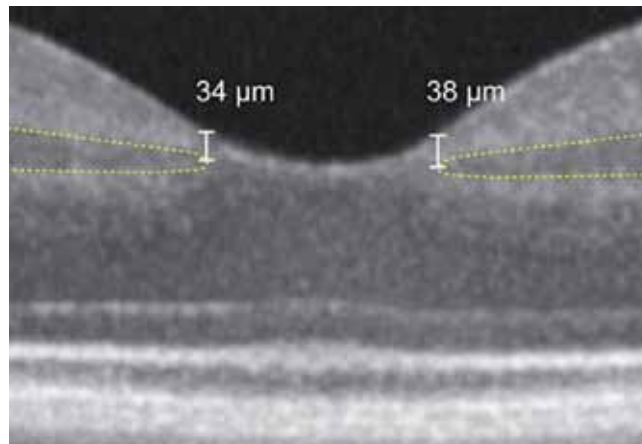


Fig. 2. An example of measurement of distance between the inner limiting membrane and the borders of the inner nuclear layer
Рис. 2. Пример оценки дистанции между внутренней пограничной мембраной и краем внутреннего ядерного слоя

The distance between the ILM and the INL edge was estimated using the horizontal B-scans (12-mm, averaging 100 scans of 1024 A-scans in each) of 36 healthy volunteers. The distance was calculated manually from the temporal and the nasal sides of the center of the fovea using Copernicus REVO software; the average of the two indices was used for the analysis. The distance between the ILM and the INL edge was determined as the length of the segment coinciding with the axis of the scanning beam and connecting the ILM and the INL edge, located closest to the center of the fovea (Fig. 2).

When testing the similarity between the areas of the INL-free zone and the FAZ for different parameters related to the displacement of the ILM segmentation lines, only the displacement of the ILM segmentation line in the direction of the IPL/INL was used. The displacement variants were tested in a group of 36 healthy volunteers using 2-μm increments within two standard deviations from the average depth of the INL. Thus, the variants of the displacement of the ILM line downward by 28, 30, 32, 34, and 36 μm were checked. Each variant of the displacement was tested in 15 volunteers from the control group. Correspondingly, for each variant, the area of the INL-free zone was calculated in ImageJ (NIH, Bethesda, USA) after scaling.

The analysis of the area of INL-free zone, the FAZ area, and their ratio was performed in a group of healthy volunteers as well as in a group of DR patients exhibiting optimal displacement of the segmentation lines (determined earlier according to the testing of variants of the

segmentation line displacement). The ratio of the INL-free area to the FAZ area was used as a diagnostic criterion for FAZ alteration.

Statistics

All data are presented as mean $\pm$ standard deviation. For statistical analysis, the software package MedCalc 18.4.1 was used. The statistical significance of the differences in the FAZ area and the ratio of the IPL/INL area to the FAZ area between healthy volunteers and patients with DR were estimated using a single-factor analysis of variance. The correlation between the FAZ area and the INL-free zone was estimated using the Spearman correlation coefficient. The Bland – Altman analysis was used to determine the optimal depth of displacement of the segmentation lines. The working capacity of the diagnostic criteria (FAZ area and the ratio of the IPL/INL area to the FAZ area) was assessed with the receiver operating characteristics (ROC) curve analysis. The threshold of statistical significance was considered to be $p < 0.05$.

RESULTS

The depth of the INL edges was analyzed in a group of healthy volunteers that included 36 people (20 men and 16 women) with an average age of 51.2 ± 11.5 years. The average distance from the ILM to the INL boundaries was 32.0 ± 2.6 μm. Based on the above-mentioned data, the optimal displacement of the ILM segmentation line was determined to be in the range of 28–36 μm. The optimal parameters for the displacement were also calculated in the same

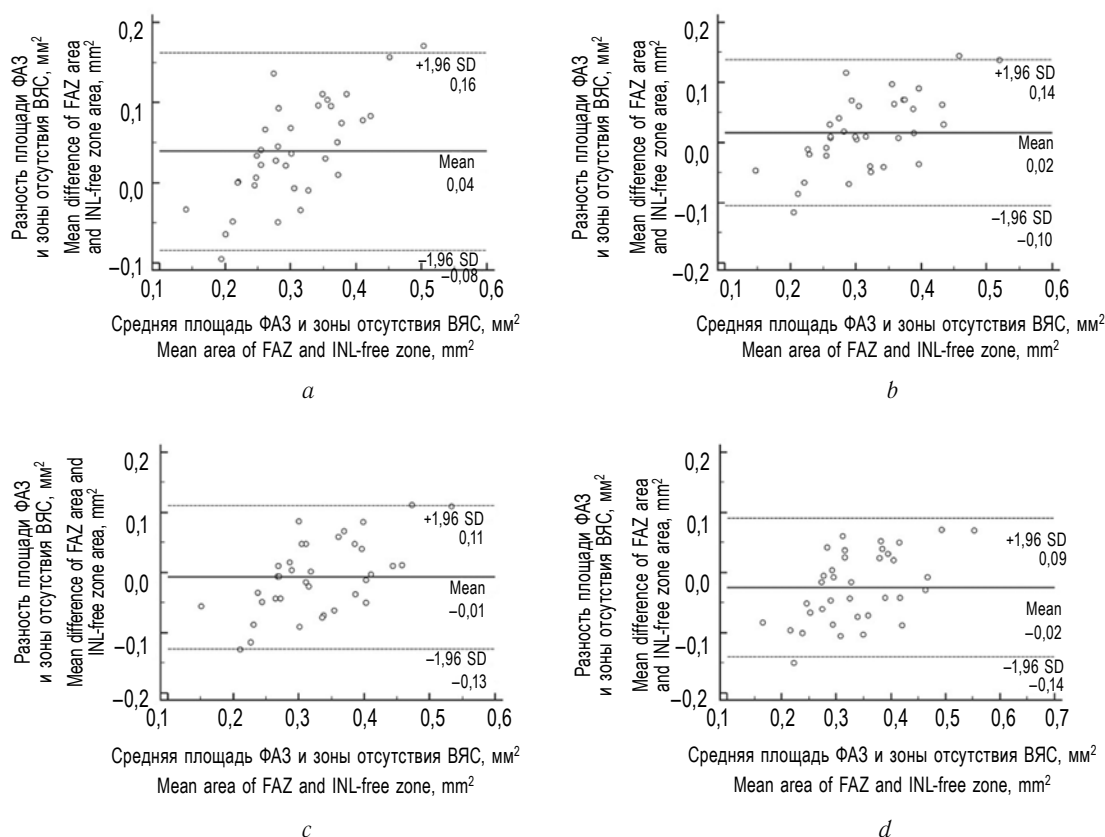


Fig. 3. Bland-Altman plots showing the agreement between the foveal avascular zone (FAZ) and the inner nuclear layer (INL)-free area in different automatic segmentation line settings: *a* – automatic segmentation line delineating the inner limiting membrane (ILM) shifted toward INL for 30 μm . (ILM = $-30\ \mu\text{m}$, IPL/INL = $0\ \mu\text{m}$); *b* – automatic segmentation line delineating ILM shifted toward INL for 32 μm (ILM = $-32\ \mu\text{m}$, IPL/INL = $0\ \mu\text{m}$); *c* – automatic segmentation line delineating ILM shifted toward INL for 34 μm . (ILM = $-34\ \mu\text{m}$, IPL/INL = $0\ \mu\text{m}$); *d* – automatic segmentation line delineating ILM shifted toward INL for 36 μm (ILM = $-36\ \mu\text{m}$, IPL/INL = $0\ \mu\text{m}$). Note the lowest mean difference between FAZ and INL-free area with automatic segmentation line delineating ILM shifted toward INL for 34 μm

Рис. 3. Анализ Бланда – Альтмана для различных вариантов смещения линии сегментации внутренней пограничной мембраны (ВПМ); *a* — смещение линии сегментации ВПМ на $-30\ \mu\text{m}$ (ВПМ = $-30\ \mu\text{m}$, внутренняя пограничная мембрана (ВПС)/внутренний ядерный слой (ВЯС) = $0\ \mu\text{m}$); *b* — смещение линии сегментации ВПМ на $-32\ \mu\text{m}$ (ВПМ = $-32\ \mu\text{m}$, ВПС/ВЯС = $0\ \mu\text{m}$); *c* — смещение линии сегментации ВПМ на $-34\ \mu\text{m}$ (ВПМ = $-34\ \mu\text{m}$, ВПС/ВЯС = $0\ \mu\text{m}$); *d* — смещение линии сегментации ВПМ на $-36\ \mu\text{m}$ (ВПМ = $-36\ \mu\text{m}$, ВПС/ВЯС = $0\ \mu\text{m}$). Отметьте наименьшее среднее значение разницы площади фовеальной аваскулярной зоны (ФАЗ) и зоны отсутствия внутреннего ядерного слоя (ВЯС) при смещении линии сегментации ВПМ на $-34\ \mu\text{m}$

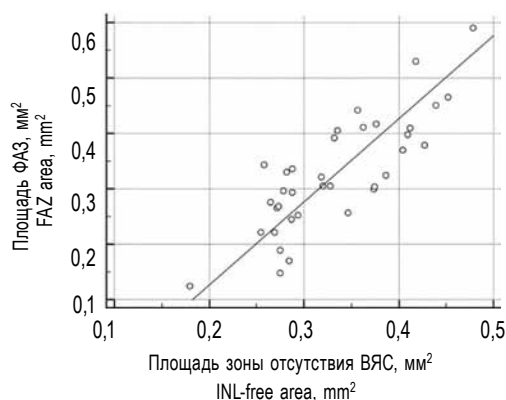


Fig. 4. Scatter plot showing a significant correlation between the foveal avascular zone (FAZ) area and inner nuclear layer (INL)-free area with automatic segmentation line delineating the inner limiting membrane shifted toward INL for 34 μm

Рис. 4. График корреляции площади фовеальной аваскулярной зоны (ФАЗ) и площади зоны отсутствия внутреннего ядерного слоя (ВЯС) при смещении линии сегментации внутренней пограничной мембраны на $-34\ \mu\text{m}$

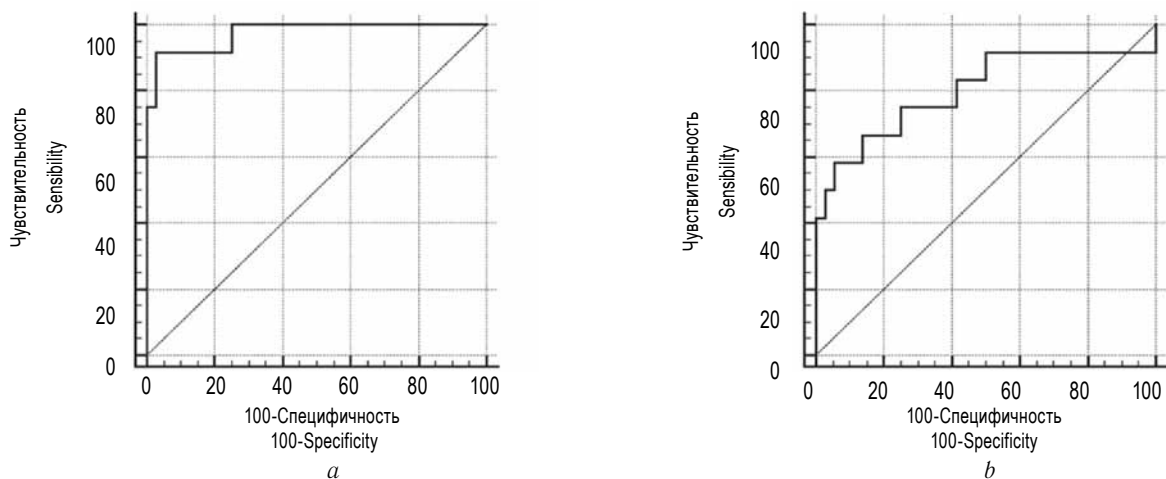


Fig. 5. Receiver operating characteristic plots demonstrating diagnostic accuracy of study criteria for mild to moderate non-proliferative diabetic retinopathy: *a* — the ratio of the inner nuclear layer (INL)-free area with automatic segmentation line delineating the inner limiting membrane shifted toward INL for 34 μm to the foveal avascular zone (FAZ); *b* — the FAZ area on optical coherence tomography angiography image

Рис. 5. ROC-анализ исследуемых критериев в диагностике диабетической непролиферативной ретинопатии лёгкой и средней степеней тяжести: *a* — отношение площади зоны отсутствия внутреннего ядерного слоя и площади фовеальной аваскулярной зоны при смещении линии сегментации внутренней пограничной мембраны на -34 мкм ; *b* — площадь фовеальной аваскулярной зоны на изображении оптической когерентной томографии ангиографии

group of volunteers. The smallest average difference in the estimation of the FAZ area was obtained through displacement of the ILM segmentation line by 34 μm , amounting to -0.007 mm^2 (CI 95%, $-0.02791-0.01330\text{ mm}^2$) (Fig. 3).

For this variant of displacement, a direct strong correlation was detected ($r = 0.97$; $p < 0.001$) between the FAZ area and INL-free zone area (Fig. 4).

The DR group included 9 patients (12 eyes), 5 men and 4 women, with an average age of 68.3 ± 6.5 years. The average values of the FAZ area in the control group and in DR patients were 0.33 ± 0.1 and $0.56 \pm 0.28\text{ mm}^2$ ($p < 0.05$), respectively; the average values of the INL-free area in the control group and in DR patients were 0.33 ± 0.07 and $0.28 \pm 0.1\text{ mm}^2$ ($p > 0.05$), respectively; the ratio of the area of the INL-free zone and the FAZ area in healthy volunteers and in the DR group were 1.08 ± 0.25 and 0.57 ± 0.19 ($p < 0.001$), respectively. A ROC analysis revealed that the FAZ area displayed a sensitivity of 66.7% and specificity of 87.1% in the diagnosis of DR, with an area under the curve of 0.8. At the same time, the ratio of the INL-free zone area to the FAZ area exhibited a sensitivity of 91.7% and specificity of 97.2% in the diagnosis of DR, with an area under the curve of 0.98 (Fig. 5).

DISCUSSION

This study demonstrates that FAZ analysis based on measurement of the ratio between the actual FAZ area and the INL-free zone has better predictive ability in diagnosing non-proliferative DR of mild to moderate severity than a conventional analysis of the FAZ area in OCTA images. This was ensured by the personalization of measurements for each individual.

Despite the fact that a large number of studies indicate the informative value of assessing the FAZ area in the diagnosis of DR and post-occlusive retinopathies, the categorization of this index between the norm and pathological changes can be problematic in certain cases. This could be due to the significant spread in normal values of this indicator. Thus, measurement of the FAZ area is more appropriate for assessing the dynamic changes in a particular patient (for example, an increase in FAZ area during the course of disease progression) and, to a lesser extent, for primary diagnosis. This study proves that an estimate of the ratio of the area of INL-free zone to the FAZ area serves as a better performance indicator in the diagnosis of mild to moderately severe non-proliferative DR and could be successfully used for primary diagnosis.

The proposed method is based on comparison of the full-face images of the OCTA area of the

INL-free zone and the area of the actual FAZ, because these indices are almost identical in the norm. Since the INL is a fairly stable structure, the difference in the areas of the INL-free zone and the FAZ reveals a pathological increase in the natural non-perfused zone (FAZ) due to ischemia. The ability to visualize the INL absence zone on the full-face OCTA image is a unique aspect of Copernicus REVO software. Simultaneous visualization of the INL-free zone and the FAZ in a single image facilitates the evaluation procedure, which is not a prerequisite for such analysis. However, this form of visualization of the investigated zones enables quick, semi-quantitative estimation. The key features of the proposed algorithm include the following:

- 1) Automatic segmentation lines ensure that the proposed type of analysis is independent of the researcher.
- 2) Standard parameters for the displacement of the segmentation lines enable easy reproduction for dynamic observation and comparison of cases. For this procedure, different segmentation lines can be employed, but the lines of segmentation of ILM and (IPL)/INL were used in this study. The advantage is the least likelihood of incorrect segmentation due to its high contrast in comparison with the vitreous body. On the other hand, the segmentation line of (IPL)/INL is located along the INL boundary, which is closest to the ILM, facilitating the accurate determination of the edge of the INL along the perimeter of macular center.

For this analysis, preservation of the foveolar contour is important, since its change tends to affect the accuracy of the automatic segmentation of the ILM and (IPL)/INL and their relationship. Hence, eyes with macular edema and abnormalities of the vitreoretinal interface (VRI) were excluded from the study. First, this is due to the fact that intra-retinal cysts, both with macular edema and VRI abnormalities, can cause an alteration in the topographic relationships between the vessels of the microvasculature and the layers of the retina, which may in turn affect the correlation between the FAZ and the INL-free zone. Second, a decrease in the signal intensity and a change in the topography of the retinal layers by micro-cysts enhance the probability of segmentation errors. Since automatic segmenta-

tion lines were used in our study to visualize the INL-free zone, their change can influence the reliability of the analysis. Third, as shown in earlier studies, a change in the VRI leads to an FAZ deformity on OCTA images [7]. Nevertheless, the described approach for eyes with macular edema and VRI abnormalities deserves further investigation. Another instance where the proposed type of analysis could cause difficulties is disorganization of the retinal internal layers (DRIL) [13], since segmentation is difficult or impossible in these cases. However, the DRIL serves as a sign of severe ischemic injury, while our approach is primarily intended for the diagnosis of the mild forms of diabetic maculopathy.

The proposed method is based on the estimation of zonal areas. Nonetheless, the simplified approach based on linear measurements of the FAZ diameter and the distance between the INL edges in one or several meridians could enable personalization of the FAZ measurement. Such a simplified variant of this analysis can be used for those tomography models, in which the visualization of the INL-free zone is difficult with the inherent software.

The advantage of a personalized approach is the potential opportunity to quantify the severity of the ischemic damage to the macula depending on the magnitude of the increase in FAZ area. However, this requires careful validation, since it is not clear whether for example a two-fold increase in FAZ area indicates a similar severity of ischemia in the eyes with small or large FAZ at baseline.

The type of analysis proposed in this report is based on data on the blood supply to the foveal zone. A number of previously published studies have established the presence of a pronounced connection between morphometric foveal parameters and the FAZ area [4, 5, 11]. Moreover, Chui et al. (2014) demonstrated the close relationship between the INL and the position of the terminal capillaries forming the FAZ, indicating that the presence of capillaries is necessary to maintain a minimum thickness ($>60\text{ }\mu\text{m}$) of the inner layers of the retina [3]. Recent studies using projection-resolved algorithms have separately visualized the middle and deep capillary plexuses located correspondingly to the inner and outer INL boundaries [2], the first of which forms the

FAZ [10]. This permits to conclude that, in the norm, the INL has a pronounced anatomical connection with the deep capillary plexus (or with middle and deep plexuses). This is quite natural, since the INL-forming neurons require intensive blood supply. That is why the discrepancy between the INL localization and the deep vascular plexus was postulated to serve as a diagnostic criterion, especially for mild ischemia, where the foveal anatomy is preserved. In severe DR, the use of FAZ as a diagnostic criterion holds less significance, since the severity of the condition could be established based on other explicit signs. For this category of patients, dynamic observation has crucial significance. On the contrary, main difficulties in the diagnosis and staging of the severity of retinopathy are associated with mild forms of the disease.

In studying different depths of segmentation lines, the displacement of the ILM segmentation line by 34 μm in the INL direction most reliably reflects the normal FAZ. Thus, using this approach, it is possible to understand the characteristics of the normal FAZ for a given patient as well as which deviations from the norm it demonstrates at a certain moment. This fact considerably augments the value of this parameter for primary diagnosis as well as for more detailed and precise monitoring in dynamics. An additional advantage of this indicator is the possibility of its application in assessing the initial changes of FAZ when the area increase is insignificant and does not exceed the limits of the normal range.

CONCLUSION

This study demonstrates superior diagnostic capabilities of a personalized FAZ analysis when compared with the classical assessment of the FAZ area in the diagnosis of non-proliferative DR of mild to moderate severity. The proposed approach is based on comparison of the areas of the INL-free zone and the actual FAZ, with the expansion of the FAZ beyond the boundaries of the INL-free zone indicating ischemic damage.

Information on funding and conflict of interest

The authors have no conflict of interest and financial interest in this study.

Contribution of authors

The concept and design of the study — D.S. Maltsev.

Collection and processing of material — D.S. Maltsev, M.A. Burnasheva.

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