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OCT Angiography Biomarkers for Predicting Visual Outcomes after Ranibizumab Treatment for Diabetic Macular Edema

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Abstract

Purpose: To correlate quantitative OCT angiography (OCTA) biomarkers with clinical features and to predict the extent of visual improvement after ranibizumab treatment for diabetic macular edema (DME) with OCTA biomarkers.

Design: Retrospective, longitudinal study in Taiwan.

Participants: Fifty eyes of 50 patients with DME and 22 eyes of 22 healthy persons, with the exception of cataract and refractive error, from 1 hospital.

Methods: Each eye underwent OCT angiography (RTVue XR Avanti System with AngioVue software version 2017.1; Optovue, Fremont, CA), and 3 × 3-mm^2 en face OCTA images of the superficial layer and the deep layer were obtained at baseline and after 3 monthly injections of ranibizumab in the study group. OCT angiography images also were acquired from the control group.

Main Outcome Measures: Five OCTA biomarkers, including foveal avascular zone (FAZ) area (FAZ-A), FAZ contour irregularity (FAZ-CI), average vessel caliber (AVC), vessel tortuosity (VT),

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HUMAN SUBJECTS: Human subjects were included in this study. The human ethics committees at the National Taiwan University Hospital approved the study. All research adhered to the tenets of the Declaration of Helsinki. The ethics committees waived the requirement of informed consent because of the retrospective nature of the study.
No animal subjects were included in this study.

and vessel density (VD), were analyzed comprehensively. Best-corrected visual acuity (BCVA) and central retinal thickness (CRT) also were obtained. Student *t* tests were used to compare the OCTA biomarkers between the study group and the control group. Linear regression models were used to evaluate the correlations between the baseline OCTA biomarkers and the changes of BCVA and CRT after treatment.

Results: Eyes with DME had larger AVC, VT, FAZ-A, and FAZ-CI and lower VD than those in the control group ($P < 0.001$ for all). After the loading ranibizumab treatment, these OCTA biomarkers improved but did not return to normal levels. Among all biomarkers, higher inner parafoveal VD in the superficial layer at baseline correlated most significantly with visual gain after treatment in the multiple regression model with adjustment for CRT and ellipsoid zone disruption ($P < 0.001$). To predict visual improvement, outer parafoveal VD in the superficial layer at the baseline showed the largest area under the receiver operating characteristic curve (0.787; $P = 0.004$). No baseline OCTA biomarkers showed any significant correlation specifically with anatomic improvement.

Conclusions: For eyes with DME, parafoveal VD in the superficial layer at baseline was an independent predictor for visual improvement after the loading ranibizumab treatment.

Diabetic macular edema (DME) is a leading cause of visual loss in patients with diabetic retinopathy (DR).[1] Antibodies against vascular endothelial growth factor (VEGF) and intravitreal steroids have demonstrated robust treatment effects on visual improvement in DME.[1–3] However, some patients do not achieve significant visual gain even after resolution of macular edema. Photoreceptor damage with ellipsoid zone disruption and macular ischemia are 2 possible reasons for poor visual improvement after the remission of macular edema.[4,5] OCT can be used to detect the severity of ellipsoid zone disruption. Macular ischemia traditionally is evaluated with fluorescein angiography (FA); however, the extent of macular ischemia can be difficult to quantify, and the ischemia around the fovea may not be revealed clearly because of the small area of involvement and capillary leakage from the adjacent area.

OCT angiography (OCTA) is a noninvasive technique that shows the retinal vascular structure with an increased resolution compared with FA. Quantified microvascular parameters also can be obtained from OCTA images. Disorganization of the retinal inner layers with a larger foveal avascular zone (FAZ) has been shown to correlate with poor visual acuity (VA) in patients with resolved DME.[6] Recently, we proposed multiple OCTA features for computer-aided classification of sickle-cell retinopathy and DR.[7–9] The purpose of this study was to establish the correlation between quantitative OCTA features and clinical testing parameters and to verify whether quantitative OCTA parameters can serve as objective factors to predict visual improvement after treatment with ranibizumab for DME. Five OCTA biomarkers, including FAZ area (FAZ-A), FAZ contour irregularity (FAZ-CI), average vessel caliber (AVC), vessel tortuosity (VT), and vessel density (VD), were analyzed comprehensively and their correlations with clinical markers, that is, best-corrected visual acuity (BCVA) and central retinal thickness (CRT), were evaluated quantitatively.

Methods

Study Population

Patients who received intravitreal ranibizumab for DME from 2 doctors (Y-.T.H. and C.-H.Y.) at the National Taiwan University Hospital, Taipei, Taiwan, and whose first injection occurred between October 2015 and September 2017 were enrolled retrospectively as the study group. The diagnostic criteria for DME were (1) DR with focal or diffuse leakage in the macular area documented by FA and (2) macular edema with the presence of retinal thickening, intraretinal cysts, intraretinal hyperreflective foci, or subretinal fluid as documented by OCT. All patients received 3 consecutive monthly intravitreal injections of ranibizumab. Examinations of BCVA and OCTA with the RTVue XR Avanti System using AngioVue software version 2017.1 (Optovue, Fremont, CA) were performed at the baseline and 1 month after the third intravitreal ranibizumab injection. Other inclusion criteria included (1) baseline BCVA between 20/400 and 20/40, (2) baseline CRT of more than 300 mm, and (3) complete data of BCVA and OCTA at baseline and 1 month after the third intravitreal ranibizumab injection. Exclusion criteria included (1) eyes with vitreomacular traction or tractional retinal detachment demonstrated by OCT, (2) eyes with choroidal neovascularization or any other retinal vascular diseases such as retinal vein occlusion documented by FA, and (3) eyes with poor en face OCTA images with a signal strength index of less than 40 because of media opacity or significant motion artifact. For patients with both eyes qualified for the study, only the eye with more severe DME at the baseline was recruited. As for the control group, we retrospectively recruited patients who visited National Taiwan University Hospital between October 2015 and September 2016; these patients did not demonstrate ocular diseases other than cataract and refractive errors. Age-matched patients were selected for the control group, and the OCTA data of 1 of their eyes were recruited for the study. This study adhered to the tenets of the Declaration of Helsinki. This study was approved by the institutional review board of the National Taiwan University Hospital, and the requirement of informed consent was waived because of the retrospective nature.

Data Acquisition

The OCT data were acquired at a 70-KHz A-scan rate with an axial resolution of approximately 5 μm and a lateral resolution of approximately 15 μm. A-scan, B-scan, and en face angiography images of both the superficial capillary plexus (SCP) and the deep capillary plexus (DCP) were collected for analysis. All of the en face angiography images were macular scans with a field of view of 3 × 3 mm; the images were generated by automated layer segmentation using the software of the OCT instrument. If the automated layer segmentation was wrong, manual segmentation was performed by 1 experienced doctor (C.-C.H.) to segment the SCP (from 3 μm below the internal limiting membrane to 15 μm below the inner plexiform layer) and the DCP (from 15 μm below the inner plexiform layer to 70 μm below the inner plexiform layer). We exported the OCTA images from the software ReVue (Optovue) and used custom-developed Matlab (Mathworks, Natick, MA) procedures with a graphical user interface for further image analysis, feature extraction, and image classification. B-scan OCT was used to observe the integrity of ellipsoid zone; images showing disruption of the ellipsoid zone line within a 1.5-mm diameter of the fovea in the

vertical or horizontal B-scan OCT were judged as positive for ellipsoid zone disruption. The signal strength index (SSI) also was recorded.

Preprocessing of OCT Angiography Images

To account for light and contrast image variation in OCTA images, several preprocessing steps for image standardization were performed before feature extraction.[7–9] All of the OCTA images were normalized to a standard window level based on the maximum and minimum intensity values to increase the overall reliability of the extracted features.

Quantitative OCT Angiography Biomarkers

Five quantitative parametersdFAZ-A, FAZ-CI, AVC, VT, and VDdwere used as OCTA biomarkers in this study for analysis. The rationale for studying each of these 5 OCTA parameters has been described in our previous publication.[7] Figure 1 shows an example of the processes involved in extracting the OCTA feature vectors. While analyzing VD, we considered vessel densities in 2 circular regions: the inner parafovea (the area between the 1-mm- and 2-mm-diameter circles) and the outer parafovea (the area between the 2-mm- and 3-mm-diameter circles). To improve the diagnostic accuracy, the segmented FAZ area was excluded when measuring VD. In this study, VD and 2 FAZ parameters were analyzed in both the SCP and DCP, whereas AVC and VT were analyzed only in the SCP because of the poor image quality in the DCP in the patients with severe macular edema.

Statistical Analysis

Best-corrected visual acuity was converted to the logarithm of the minimum angle of resolution (logMAR) for statistical analysis. Student *t* tests were used to compare the OCTA biomarkers between the study group at baseline and the control group, and paired *t* tests were used to compare the baseline and posttreatment OCTA biomarkers in the study group. Pearson correlation analysis was used to evaluate the correlations between OCTA biomarkers, BCVA, CRT, and SSI at baseline. Linear regression models were used to evaluate the predicting effects of OCTA biomarkers for changes in BCVA and CRT after 3 injections of ranibizumab. Baseline BCVA, CRT, and ellipsoid zone disruption were adjusted in the model for changes in BCVA, and baseline CRT was adjusted in the model for changes in CRT. The predictability for visual improvement (change in BCVA of <0 logMAR) was examined for each OCTA biomarker using receiver operating characteristic curve analysis with adjustment for baseline BCVA, CRT, and ellipsoid zone disruption, and the area under the receiver operating characteristic curve was calculated. For Student *t* tests and paired *t* tests, a *P* value of less than 0.05 was considered statistically significant. For correlation analysis, Bonferroni correction was used to adjust for the effect of multiple comparisons so that a *P* value of less than 0.005 was considered statistically significant. SAS software version 9.4 (SAS Institute, Inc, Cary, NC) was used for all statistical analyses.

Results

Fifty eyes from 50 patients were included in the study group, and 22 eyes from 22 age-matched persons were included in the control group. Figure 2 shows the flow chart for patient recruitment of the study group. The mean age was 61.7 ± 10.6 years in the study

group and 60.9 ± 13.5 years in the control group ($P = 0.80$). Twenty-seven of 50 patients in the study group were women, and 14 of 22 participants in the control group were women ($P = 0.45$).

OCT Angiography Biomarkers

Table 1 shows the OCTA biomarkers of the study group at baseline and after treatment and those of the control group. The FAZ-A, FAZ-CI, AVC, and VT in the study group at baseline all were larger than those in the control group ($P < 0.001$ for all). As for VD, the values of the inner and outer parafovea in both the SCP and DCP in the study group at baseline all were lower than those in the control group ($P < 0.001$ for all). After treatment with ranibizumab, the AVC and FAZ-A both significantly decreased ($P < 0.001$ for all); the VD also increased significantly ($P < 0.05$ for all). However, the values still did not return to the normal levels when compared with those of the control group.

Correlations among OCT Angiography Biomarkers, Best-Corrected Visual Acuity, Central Retinal Thickness, and Signal Strength Index at Baseline

For the study group, the mean BCVA at baseline was 0.73 ± 0.39 logMAR (range, 0.15–1.70 logMAR), and the mean CRT at the baseline was 458±157 μm (range, 280–999 μm). Table 2 shows the results of Pearson correlation analysis among OCTA biomarkers, BCVA, CRT, and SSI. A poorer SSI was correlated with a poorer BCVA ($P = 0.008$) and a thicker CRT ($P < 0.001$). A lower parafoveal VD in either the SCP or the DCP was correlated with a poorer BCVA, a thicker CRT, and a poorer SSI ($P < 0.05$ for all). A larger AVC was correlated with a poorer BCVA ($P = 0.036$), and a higher VT was correlated with a larger SSI ($P = 0.005$). Foveal avascular zone contour irregularity was less correlated with BCVA, CRT, or SSI.

Correlations among OCT Angiography Biomarkers and Diabetic Retinopathy Severity at Baseline

Among the 50 eyes in the study group, 16 demonstrated moderate nonproliferative DR, 8 demonstrated severe nonproliferative DR, and 26 demonstrated proliferative DR (PDR). As shown in Table 3, the more severe the DR, the less the VDs at both the inner and outer parafovea in both the SCP and DCP ($P < 0.05$ for all). The extent of VT was the least in the PDR group ($P = 0.010$). Foveal avascular zone area, FAZ-CI, and AVC did not show significant differences among the 3 levels of DR severity ($P > 0.05$ for all).

Correlations among Baseline OCT Angiography Biomarkers and Visual and Anatomic Improvement after Ranibizumab Treatment

After 3 consecutive injections of ranibizumab, the mean BCVA of the study group improved from 0.73±0.39 logMAR to 0.56±0.39 logMAR (range, 0e1.52 logMAR; $P < 0.001$), and the mean CRT decreased from 458±157 μm to 319±102 μm (range, 161–641 μm; $P < 0.001$). Table 4 shows the results of linear regression analysis for the predicting effects of baseline OCT biomarkers for the changes in either logMAR BCVA or CRT after treatment. After adjustment for CRT and ellipsoid zone disruption at baseline, higher inner parafoveal VD in the SCP at baseline predicted better visual gain after the loading ranibizumab treatment ($P < 0.001$). Eyes with higher VT at baseline also tended to show better visual gain after

treatment ($P = 0.004$). Contrarily, none of the baseline OCTA biomarkers were correlated with change in CRT after the loading treatment ($P > 0.05$ for all).

Receiver Operating Characteristic Curve for Predicting Visual Improvement after Ranibizumab Treatment

Table 5 shows the results of the receiver operating characteristic curve analysis for predicting visual improvement after the loading ranibizumab treatment. Among the baseline OCTA biomarkers, the outer parafovea in the superficial layer showed the best predictive value for visual improvement after treatment after adjustment for baseline BCVA, CRT, and ellipsoid zone disruption (area under the receiver operating characteristic curve, 0.787; $P = 0.004$; Fig 3).

Comparisons of OCT Angiography Biomarkers among Different Treatment Response Groups

According to the results after the loading ranibizumab treatment, the patients in the study group were separated into 3 subgroups: eyes with both visual and anatomic improvement (28 eyes), those with anatomic improvement only (10 eyes), and those with no visual or anatomic improvement (12 eyes). As shown in Table 6, eyes with both visual and anatomic improvement after the loading ranibizumab treatment showed the highest SSI and VDs, whereas those with anatomic improvement but no visual improvement after treatment showed the lowest SSI and VDs among the 3 groups. However, the differences were significant only for SSI and the inner parafovea in the SCP between those with both visual and anatomic improvement and those with anatomic improvement only ($P = 0.013$ and $P = 0.025$, respectively).

Discussion

In this study, we first investigated the correlations among quantitative OCTA parameters and BCVA and CRT at baseline. We found that poorer VD in both the SCP and DCP at the parafoveal area was correlated with both poorer BCVA and thicker CRT. This finding is consistent with a previous study of DR.[10] However, in DME, this finding may suggest that poorer parafoveal vascular perfusion itself could result in poorer vision, or it could be caused by macular edema, which is the real reason for poorer vision. Therefore, when investigating the correlations between baseline OCTA parameters and visual improvement after ranibizumab treatment, we not only adjusted for baseline BCVA, but also for baseline CRT, because it could affect both BCVA and vessel density. Ellipsoid zone disruption also was adjusted in the regression models because of its effect on poor vision. We found that after adjusting for baseline BCVA, CRT, and ellipsoid zone disruption, lower parafoveal VD in the superficial layer was correlated with poorer visual improvement after treatment with ranibizumab. This demonstrated that poorer vascular perfusion itself resulted in visual impairment; even after the macular edema subsided, the vision of the eyes with macular hypoperfusion might not improve significantly. Receiver operating characteristic curve analysis also showed that outer parafoveal VD in the superficial layer could predict visual improvement after ranibizumab treatment (area under the receiver operating characteristic

curve, 0.821). Such a result is useful for offering patients with DME reasonable expectations for treatment effects after undergoing anti-VEGF treatment.

OCT angiography has been an effective and noninvasive tool for investigating retinal vascular diseases such as DR. Previous studies have shown that increased FAZ-A or FAZ-CI, increased nonperfusion area, decreased VD, and decreased fractal dimension of the central macula were associated with the worsening of DR.[11–16] It also has been shown that a larger FAZ-A and a poorer VD were associated with poorer VA in patients with DR.[10,17] In this study, we also found that decreased VD was associated with the worsening of DR. As for the clinical treatment for DME, ophthalmologists mostly focus on treating macular edema. However, not all patients who have achieved macular edema resolution show significant improvement in VA. It is possible that macular ischemia, in addition to macular edema and photoreceptor disruption, also contribute to the poor vision in these patients. Moein et al[6] showed that a larger FAZ was correlated with poor VA in patients with resolved DME. However, whether baseline OCTA characteristics can be used to predict the visual improvement after treatment for DME has not been studied until the present study.

Durbin et al[18] showed that VD in the superficial layer, not the deep layer, was correlated with VA in DR. Our study also showed similar findings. It is possible that the projection artifact affects the deep layer more than the superficial layer. In addition, because all these patients had macular edema, the decay of image signals is more severe as the light source penetrates deeper in the retina. Although in the present study the VDs in the deep retinal layer at baseline also showed a trend of correlations with visual improvement after treatment, the significance was less than that in the superficial layer. With improvements in the technique for projection artifact removal and the 3 distinct retinal capillary plexuses being visualized better,[19] we expect that the analysis for the intermediate capillary plexus and DCP would offer more reliable results.

In addition to VD, we found that eyes with higher VT in the superficial layer at baseline tended to achieve better visual improvement after ranibizumab treatment. However, we also found that eyes with DME showed higher VT than healthy control eyes and that VT decreased after ranibizumab treatment. We believe that macular edema results in higher VT because of the distortion of the retinal structure. However, considering the algorithm, macular hypoperfusion and capillary dropout should result in a decrease in VT. This is shown by the positive correlation between VT and VD at the inner parafovea ($\gamma = 0.33$; $P = 0.031$) and the outer parafovea ($\gamma = 0.39$; $P = 0.012$) in the superficial layer in the present study. We hypothesize that the correlation between VT at baseline and visual improvement after treatment was confounded by VD at baseline. Therefore, in the multiple regression analysis, only VD at the outer parafovea, but not VT, was selected and was a significant factor in the model. Lee et al[20] also showed that VT increased in nonproliferative DR but decreased in PDR. Such findings also match our hypothesis.

In the present study, we found that FAZ-A significantly decreased after ranibizumab treatment. This may have been the result of the nonperfused parafoveal capillary network becoming reperfused again after the macular edema subsided or of the capillary network masked by severe macular edema being detected better by OCTA after the macular edema

subsided. However, FAZ-A and FAZ-CI were not correlated significantly with VA at baseline or with visual improvement after treatment. Balaratnasingam et al[17] showed that the area of the FAZ is correlated significantly with VA in DR after adjusting for ellipsoid zone disruption. However, only 38 of the 65 eyes in their study had macular edema, and the extent of macular edema was not adjusted in the analysis. Although we found in the present study that both the mean FAZ-A and FAZ-CI both were larger in eyes with DME than those in normal eyes, the size and contour of FAZ may vary widely among normal populations.[21] Lee et al[22] found that DME patients who show a poor response to anti-VEGF treatment demonstrate a larger FAZ-A in the DCP. We also found that the average FAZ-A in the DCP was largest for eyes with good anatomic but poor visual improvement than those showing both visual and anatomic improvement or those showing no improvement at all, but the differences were not statistically significant ($P = 0.78$ and $P = 0.41$, respectively). Our results showed that FAZ-A or FAZ-CI could not be used to predict visual improvement after ranibizumab treatment in eyes with DME.

It is interesting that the present study showed that the AVC at baseline in the group without anatomic improvement was smaller than in the group showing anatomic improvement. Kim et al[12] found that AVC increases as the extent of DR becomes more severe. It may be the result of the more extensive dropout of small-caliber capillaries, leaving only large-caliber arterioles and venules. It also may be the result of vascular dilatation caused by VEGF. For eyes with VEGF-induced vascular dilatation, it may be implied that the intraocular level of VEGF before treatment is high, and anti-VEGF thus eliminates VEGF-induced complications, including vascular dilatation and leakage. As for the eyes without anatomic improvement after ranibizumab treatment, it is possible that VEGF does not play an important role in inducing DME or that the VEGF level is low; therefore, the vessels are less dilated because of the relatively small VEGF effect.

There were some limitations in this study. First, macular edema itself may affect the signal strength of OCTA measurement. Therefore, those with very severe macular edema would have been excluded in this study because of low SSI. Second, as mentioned previously, the projection artifact may interfere more with the imaging quality of the deep retinal layer than of the superficial layer. With future advancements in OCTA hardware and software, we will be able to identify more precise predictors for the treatment outcomes of DME.

In conclusion, we found that parafoveal vessel density in the superficial retinal layer at baseline was an independent predictor for visual improvement after the loading ranibizumab treatment in eyes with DME. OCT angiography offers measurement for VD in the macula and could be used to predict the visual prognosis of anti-VEGF treatment in DME.

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Abbreviations and Acronyms:

AVC	average vessel caliber
BCVA	best-corrected visual acuity
CRT	central retinal thickness
DCP	deep capillary plexus
DME	diabetic macular ede
DR	diabetic retinopathy
FA	fluorescein angiography
FAZ	foveal avascular zone
FAZ-A	foveal avascular zone area
FAZ-CI	foveal avascular zone contour irregularity
logMAR	logarithm of the minimum angle of resolution
OCTA	OCT angiography
PDR	proliferative diabetic retinopathy
SCP	superficial capillary plexus
SSI	signal strength index
VA	visual acuity
VD	vessel density
VEGF	vascular endothelial growth factor
VT	vessel tortuosity

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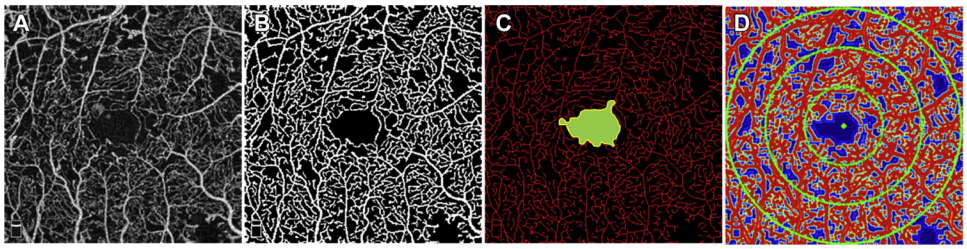

Figure 1.

Representative images for quantitative analysis: (**A**) original OCT angiography analysis, (**B**) extracted vessel map for measuring average vessel caliber and vessel tortuosity, (**C**) skeleton map showing segmented foveal avascular zone and its boundary, and (**D**) fractal dimension image used for measuring vessel density. The green circles show 3 circular areas of 1 mm, 2 mm, and 3 mm in diameters, respectively.

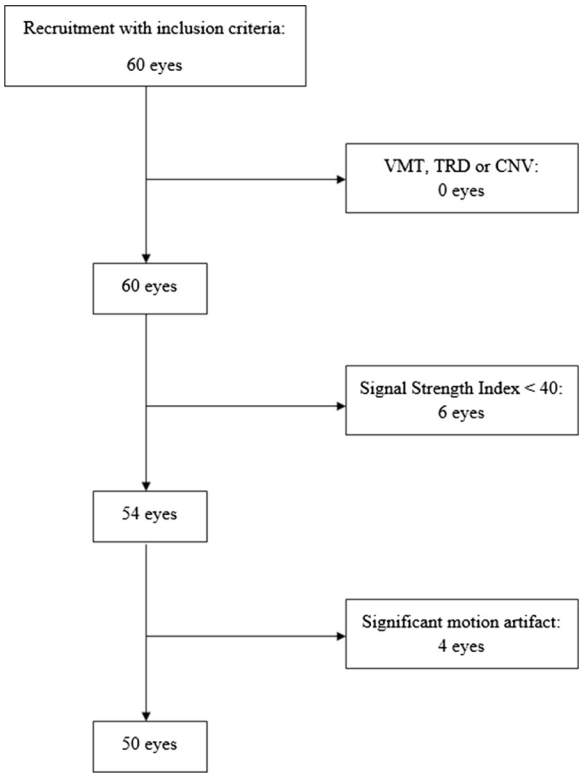

Figure 2.

Flow chart showing patient recruitment. CNV = choroidal neovascularization; TRD = tractional retinal detachment; VMT = vitre omacular traction.

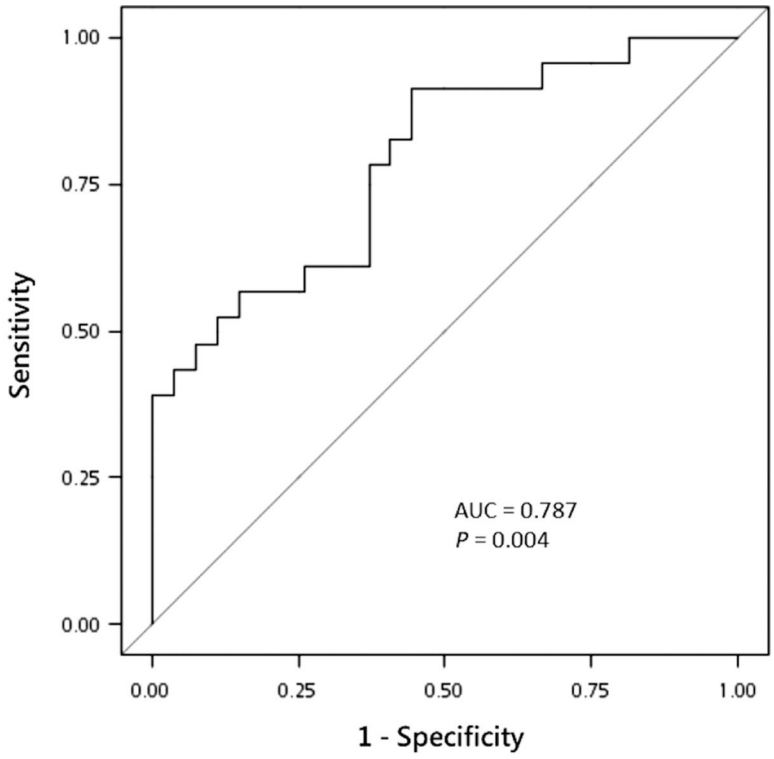

Figure 3.

Receiver operating characteristic curve showing vessel density in the outer parafovea of the superficial retinal layer in predicting visual improvement after the loading ranibizumab treatment for diabetic macular edema. AUC = area under the receiver operating characteristic curve.

Table 1.

OCT Angiography Parameters at Baseline and after 3 Consecutive Injections of Ranibizumab in the Study Group and the Control Group

				***P* Value**		
	Study Group at Baseline	**Study Group after Treatment**	**Control Group**	***Baseline vs. after Treatment***	***Baseline vs. Control Group***	***After Treatment vs. Control Group***
Superficial layer						
FAZ area (mm^2)	0.68 ±0.28	0.47±0.20	0.35±0.08	<0.001	<0.001	<0.001
FAZ circularity index	1.38±0.10	1.34±0.12	1.16±0.10	0.15	<0.001	<0.001
Average vessel caliber	27.44±4.61	26.27±3.84	19.73±3.39	<0.001	<0.001	<0.001
Vessel tortuosity	10.60±1.88	10.31 ±2.02	6.98±1.37	0.17	<0.001	<0.001
Vessel density						
Inner parafovea	42.14±8.82	44.62±8.53	51.84±5.16	0.034	<0.001	<0.001
Outer parafovea	43.23±8.92	47.03±9.15	51.45±2.79	0.006	<0.001	0.003
Deep layer						
FAZ area (mm^2)	0.75±0.32	0.52±0.22	0.43±0.05	<0.001	<0.001	0.012
FAZ circularity index	1.43±0.11	1.37±0.11	1.19±0.10	0.004	<0.001	<0.001
Vessel density						
Inner parafovea	41.54±8.89	45.34±9.81	48.59±3.51	0.002	<0.001	0.043
Outer parafovea	45.03±9.47	49.26±10.39	53.00±3.71	0.02	<0.001	0.028

FAZ = foveal avascular zone.

Table 2.

Pearson Correlation Analysis among OCT Angiography Biomarkers, Best-Corrected Visual Acuity, Central Retinal Thickness, and Signal Strength Index at Baseline

	Best-Corrected Visual Acuity (Logarithm of the Minimum Angle of Resolution)		Central Retinal Thickness (μm)		Signal Strength Index	
	Coefficient	P *Value*	*Coefficient*	P *Value*	*Coefficient*	P *Value*
Signal strength index	−0.37	0.008	−0.51	<0.001	—	—
Superficial layer						
FAZ area (mm^2)	−0.02	0.87	−0.02	0.88	0.27	0.065
FAZ circularity index	0.29	0.053	0.23	0.12	−0.16	0.29
Average vessel caliber	0.32	0.036	0.03	0.83	−0.03	0.84
Vessel tortuosity	0.03	0.87	−0.16	0.31	0.43	0.005
Vessel density						
Inner parafovea	−0.36	0.009	−0.28	0.042	0.62	<0.001
Outer parafovea	−0.38	0.007	−0.32	0.023	0.61	<0.001
Deep layer						
FAZ area (mm^2)	−0.03	0.84	−0.12	0.42	0.31	0.039
FAZ circularity index	0.13	0.40	0.40	0.005	−0.19	0.20
Vessel density						
Inner parafovea	−0.38	0.007	−0.40	0.004	0.47	<0.001
Outer parafovea	−0.53	<0.001	−0.40	0.004	0.64	<0.001

FAZ = foveal avascular zone; — = no data available.

Table 3.

OCT Angiography Parameters at Baseline and after 3 Consecutive Injections of Ranibizumab in the Study Group and the Control Group

	Moderate Nonproliferative Diabetic Retinopathy (n = 16)	Severe Nonproliferative Diabetic Retinopathy (n = 8)	Proliferative Diabetic Retinopathy (n = 26)	*P* Value
Superficial layer				
FAZ area (mm^2)	0.76±0.28	0.78±0.23	0.58±0.27	0.058
FAZ circularity index	1.36±0.08	1.41±0.11	1.38±0.12	0.40
Average vessel caliber	28.14±4.53	25.04±5.29	27.86±4.30	0.47
Vessel tortuosity	11.33±1.68	11.16± 1.19	9.68±1.97	0.010
Vessel density				
Inner parafovea	46.96±8.01	45.30±5.59	38.20±8.42	0.004
Outer parafovea	48.02±9.28	43.80±6.56	40.11±8.21	0.021
Deep layer				
FAZ area (mm^2)	0.78±0.31	0.69±0.34	0.75±0.33	0.77
FAZ circularity index	1.41 ±0.08	1.46±0.07	1.44±0.13	0.21
Vessel density				
Inner parafovea	47.37±8.46	40.30±5.06	38.33±8.46	0.009
Outer parafovea	50.54±9.68	47.79±9.26	40.78±7.41	0.004

FAZ = foveal avascular zone.

Table 4.

Linear Regression Analysis for the Correlations between OCT Angiography Biomarkers at Baseline and Visual and Anatomic Improvement after the Loading Ranibizumab Treatment

	Change in Best-Corrected Visual Acuity (Logarithm of the Minimum Angle of Resolution)		Change in Central Retinal Thickness (μm)	
	Coefficient	**P *Value***	***Coefficient***	**P *Value***
Superficial layer				
FAZ area (mm^2)	−0.26	0.082	−73.44	0.19
FAZ circularity index	0.16	0.72	36.33	0.82
Average vessel caliber	0.016	0.094	6.03	0.071
Vessel tortuosity	−0.064	0.004	−19.42	0.017
Vessel density				
Inner parafovea	−0.016	<0.001	−1.72	0.34
Outer parafovea	−0.009	0.067	−1.64	0.36
Deep layer				
FAZ area (mm^2)	−0.10	0.48	−79.64	0.11
FAZ circularity index	−0.24	0.58	3.27	0.98
Vessel density				
Inner parafovea	−0.009	0.074	−0.86	0.65
Outer parafovea	−0.010	0.047	−0.86	0.62

FAZ = foveal avascular zone.

Table 5.

Area under the Receiver Operating Characteristic Curve for Predicting Visual Improvement after the Loading Ranibizumab Treatment

Baseline OCT Angiography Biomarkers	Area under the Receiver Operating Characteristic Curve	*P* Value
Superficial layer		
FAZ area (mm^2)	0.624	0.20
FAZ circularity index	0.604	0.69
Average vessel caliber	0.653	0.11
Vessel tortuosity	0.755	0.026
Vessel density		
Inner parafovea	0.765	0.007
Outer parafovea	0.787	0.004
Deep layer		
FAZ area (mm^2)	0.597	0.49
FAZ circularity index	0.591	0.99
Vessel density		
Inner parafovea	0.622	0.27
Outer parafovea	0.696	0.068

FAZ = foveal avascular zone.

Table 6.

Baseline Characteristics and OCT Angiography Biomarkers among Different Treatment Response Groups

Characteristic	Both Visual and Anatomic Improvement	Anatomic but No Visual Improvement	No Visual or Anatomic Improvement	*P* Value		
				Visual and Anatomic Improvement vs. Anatomic but No Visual Improvement	*Visual and Anatomic Improvement vs. No Visual or Anatomic Improvement*	*Anatomic but No Visual Improvement vs. No Visual or Anatomic Improvement*
BCVA (logMAR)	0.80±0.47	0.74±0.27	0.62±0.33	0.69	0.19	0.23
CRT (μm)	473±176	475±172	400±89	0.97	0.20	0.47
Signal strength index	56.0±9.9	47.6±8.2	51.6±5.6	0.013	0.15	0.29
Superficial layer						
FAZ area (mm^2)	0.73±0.27	0.62±0.26	0.63±0.31	0.31	0.32	0.94
FAZ circularity index	1.38±0.10	1.38±0.08	1.38±0.13	0.86	0.82	0.97
Average vessel caliber	26.72±4.96	30.04±3.66	27.11±4.09	0.081	0.82	0.17
Vessel tortuosity	11.13±1.63	9.87±2.58	9.99±1.58	0.10	0.10	0.89
Vessel density						
Inner parafovea	44.29±8.35	37.02±9.56	41.40±8.02	0.025	0.33	0.24
Outer parafovea	45.58±8.16	40.49±10.94	40.02±7.79	0.12	0.070	0.90
Deep layer						
FAZ area (mm^2)	0.76±0.33	0.80±0.34	0.68±0.29	0.78	0.49	0.41
FAZ circularity index	1.43±0.10	1.42±0.13	1.43±0.12	0.82	0.95	0.88
Vessel density						
Inner parafovea	41.73±8.26	38.59±9.36	43.55±10.01	0.34	0.56	0.20
Outer parafovea	45.97±9.72	42.26±8.38	45.13±10.04	0.30	0.80	0.49

BCVA = best-corrected visual acuity; CRT = central retinal thickness; FAZ = foveal avascular zone; logMAR = logarithm of the minimum angle of resolution.