BMC Ophthalmology

RESEARCH Open Access

Predictive value of optical coherence tomography angiography in management of diabetic macular edema

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Abstract

Background Optical coherence tomography angiography (OCTA) is a relatively new extension of Optical coherence tomography (OCT) that generates non-invasive, depth-resolved images of the retinal microvasculature which allows for the detection of various features of diabetic retinopathy.

Objectives This study aimed to detect biomarkers that may predict an early anatomical response to the treatment of diabetic macular edema (DME) with intravitreal ranibizumab (IVR) by means of OCTA.

Patients and methods This prospective interventional study was undertaken on 111 eyes of 102 naïve participants who had diabetic macular edema; enrolled patients were evaluated by taking a complete ophthalmologic history, examination and investigations by use of a pre-designed checklist involving Optical Coherence Tomography Angiography.

Results Regarding the best corrected visual acuity (BCVA) the Mean ± SD was 0.704 ± 0.158 preoperatively and 0.305 ± 0.131 postoperatively in good responder patients; and was 0.661 ± 0.164 preoperatively and 0.54 ± 0.178 postoperatively in poor responders. The central macular thickness (CMT) was 436.22 ± 54.66 µm preoperatively and 308.12 ± 33.09 µm postoperatively in good responder patients; and was 387.74 ± 44.05 µm preoperatively and 372.09 ± 52.86 µm postoperatively in poor responders. By comparing the pre injection size of the foveal avascular zone area (FAZ-A) in both groups, it found that the mean ± SD of FAZ-A was 0.297 ± 0.038 mm in good responder patients compared to 0.407 ± 0.05 mm in non-responder patients. The preoperative superficial capillary plexus (SCP) foveal vascular density (VD) was 24.02 ± 3.01% in good responder patients versus 17.89 ± 3.19% um in poor responders. The preoperative SCP parafoveal VD was 43.06 ± 2.67% in good responder patients versus 37.96 ± 1.82% um in poor responders. The preoperative deep capillary plexus (DCP) foveal VD was 30.58 ± 2.89% in good responder patients versus 25.45 ± 3.14% in poor responders. The preoperative DCP parafoveal VD was 45.66 ± 2.21% in good responder patients versus 43.26 ± 2.35% um in poor responders, this was statistically significant.

Conclusion OCTA offers an accurate measurement for VD in the macula as well as the FAZ-A which could be used to predict an early anatomical response of anti-VEGF treatment in DME.

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Keywords Predictive value, Optical coherence tomography angiography, Diabetic macular edema

Introduction

Visual impairment can occur as a consequence of diabetic maculopathy, which typically presents itself as edema or ischemia in individuals with diabetes. Foveal-affecting central involved macular edema is the prevailing etiology of impairment in vision among individuals with diabetes [1, 2].

DME is an ocular complication that arises from an impairing of the blood-retinal barrier brought about by elevated blood glucose levels. The aforementioned disturbance leads to the extravasation of fluid from the vessels of the retina into the adjacent neural retina [3].

A protein that is secreted, vascular endothelial growth factor (VEGF) promotes development, inflammation, and angiogenesis; it is also associated with pathological angiogenesis [4].

Furthermore, while diabetic macular edema substantially contributes to retinal origin visual impairment, it is also among the most easily treatable conditions. Approval of the currently available intraocular anti-angiogenic and glucocorticoid agents is predicated on their proven capacity to reduce macular edema and consequently enhance visual acuity [5].

Individuals who have been diagnosed with DME are presently routinely treated with cytokine-targeting intravitreal injections. However, among patients with DME, the efficacy of anti-VEGF injections varies, and certain agents impose a greater financial burden [6].

Clinicians may be better prepared to contemplate alternative therapies if they are able to manage treatment expectations and identify patients who are susceptible to a late or inadequate response to treatment [7].

Numerous biomarkers that have been suggested as possible predictors of the anatomical and functional response of patients with DME to anti-VEGF therapy have been categorized via OCT imaging [8]. Illustrative instances of these biomarkers include the morphological configuration of DME and the recognition of disarray within the inner retinal layers [9].

An improvement over optical coherence tomography (OCT), optical coherence tomography angiography (OCTA) produces depth-resolved, non-invasive images of the retinal microvasculature. Through the utilization of this methodology, it becomes feasible to differentiate a multitude of characteristics that are associated with diabetic retinopathy (DR). These characteristics comprise the degree of hypoperfusion in the retina, the vascular density (VD) in the superficial and deep capillary plexuses (SCP and DCP), as well as the measurements of the foveal avascular zone area (FAZ-A) [10].

A number of OCTA-derived parameters have been linked in recent studies to the anatomical and functional response to anti-VEGF therapy for patients with DME [11].

The objective of this study was to identify biomarkers that might be able to forecast an early anatomical response to intravitreal ranibizumab (IVR) for DME using OCTA.

Subjects and methods

Patients

At the hospitals of Menoufia University, 111 eyes of 102 naïve participants who presented with diabetic macular edema were the subjects of a prospective interventional study. The study was showed within the Department of Ophthalmology of the Faculty of Medicine. Following a briefing on the scientific procedure and medical research, all participants were required to provide informed consent. The inquiry was conducted in adherence to the Helsinki Declaration and the Code of Ethics for Human Research of the World Medical Association. Following the acquisition of approval from the Institutional Review Board (IRB) 2/2021 OPHT5, the trial was executed.

Inclusion criteria included naïve patients between the ages of 30 and 70 who were diagnosed with type 2 diabetes mellitus; patients with DME with central macular thickness of >300 μm as determined by OCT; and cases with a BCVA ranging from 6/60 to 6/9 and an OCTA scan quality of 5 or higher.

Patients who exhibited any of the subsequent conditions were ineligible: Individuals diagnosed with type 1 diabetes. Individuals who have a medical history of retinal diseases that may affect the outcomes of retinal vasculature imaging, including but not limited to retinal vein occlusions, prior intravitreal injections, macular laser treatment or macular edema not caused by diabetes; patients with proliferative diabetic retinopathy; patients with significant media opacities such as vitreous hemorrhage or dense cataract; and patients who have undergone vitreoretinal surgery.

Methods

In order to evaluate enrolled patients, a comprehensive ophthalmologic history, examination, and investigations were performed in accordance with a pre-established checklist and a database computer program specifically developed for data entry and analysis.

Visual acuity assessment Best corrected visual acuity (BCVA) was assessed subsequent to objective refraction using the Autoref/keratometer ARK-1 (NIDEK Co, Aichi,

Japan 2013). In order to facilitate statistical analysis, BCVA measurements were transformed into their logarithmic equivalents at the minimum angle of resolution (LogMAR).

Slit-lamp biomicroscopic examination (SL-D7 Topcon, Tokyo, Japan) full examination of the anterior segment was performed.

Intra-ocular pressure measurement using Goldman applanation tonometer. **(Shin Nippon, Japan)**.

Fundus examination: By Indirect ophthalmoscope (**Model AAIO-7 Appasamy Associates 2014, India**). Volk's non-contact double aspheric biconvex lens (power: + 90).

Acquisition of optical coherence tomography angiography

An OCTA scan was done on each eye prior to the intervention. The spectral domain system RTVue-XR Avanti (Optovue Inc., Fremont, CA, USA; software versions 2017,1,0,151) was utilized to acquire the scans. The deep and superficial capillary plexuses as well as the FAZ were imaged using OCTA at baseline and three months after ranibizumab three injections with one month interval. The acquisition of an image centered on the fovea at a distance of 6 mm involved the acquisition of the macula. DCP and SCP segmentation were executed with the assistance of the integrated OCTA software. Eyes that exhibited blink artifacts, inadequate fixation leading to image doubling or motion artifacts, localized signal loss due to media opacities, or significant segmentation errors (SSI=less than five) were excluded from the analysis. The error was eradicated by manually correcting minor segmentation errors utilizing the in-built machine software in conjunction with the corresponding structural OCT B-scans. From the en face OCTA two strata, namely the superficial retinal capillaries and deep retinal capillaries, were extracted and incorporated into our analysis. The OCT system's software autonomously segmented the layers of the vessels. In order to discern the layers of retinal tissue, standard automatic segmentation was applied to OCT intensity images by analyzing their volume. The FAZ was computed automatically through the utilization of the machine's built-in software.

Intravitreal injection of ranibizumab

Intra-vitreal injections were performed of 0.5 mg ranibizumab (Lucentis®, Novartis Pharma AG., Basel, Switzerland) injected intravitreally through the pars plana using a 30-gauge needle; A one-month interval separate each of the three intravitreal injections of ranibizumab.

Post-operative follow up

All patients underwent examination using OCTA one month after their last injection. The results were statistically presented in various ways, comparing pre-injection and post-injection findings.

Main outcome measures included

This analysis takes into account the foveal avascular zone area (FAZ-A), best-corrected visual acuity (BCVA), central macular thickness (CMT), foveal and parafoveal vascular density (SCP), and foveal and parafoveal vascular density (VD) of the deep capillary plexus (DCP).

Treatment response

By analyzing the anatomical response of the eyes to IVR injections, two distinct groups of eyes were identified. Eyes that experienced a central retinal thickness (CMT) reduction of 50 μm or more subsequent to the administration of three monthly injections of IVR exhibited an early anatomical response to the treatment. Subsequently, these eyes were compared to those in which CMT progression was either unaffected or adverse despite treatment. At baseline and following three monthly injections of IVR, the SCP and DCP of the foveal, parafoveal, and FAZ regions of the two groups were compared.

Analysis of OCTA images

Automatic FAZ and VD measurements were obtained for the SCP and DCP prior to and after the three injections of IVR using the integrated Early Treatment Diabetic Retinopathy Study (ETDRS) map. To achieve this, a map comprising nine regions was utilized, with the FAZ serving as the manual center. Multiplying the result by 100 after dividing the sum of the pixels occupied by blood vessels in a given region by the total number of pixels in that region yielded the VD.

Statistical analysis

For data analysis, SPSS® Statistics version 22.0 (IBM Corp, Armonk, NY) was utilized. Mean (±SD) values are utilized to represent continuous variable data. In order to conduct the analysis, the visual acuities were converted from Snellen scales to the log minimum angle of resolution (LogMAR) scale. Following the assessment of normality utilizing the Shapiro–Wilk test, data that followed a normal distribution were examined and compared utilizing the t-test of student. Conversely, non-normally distributed data were analyzed and compared using the non-parametric Mann–Whitney U and Wilcoxon Signed Ranks tests. The chi-square test was applied to categorical data for analysis. The relation among every ocular parameter and VD and FAZ-A was evaluated through the implementation of univariate linear regression. The obtained findings were considered significant at the 5%

Table 1 Distribution of the studied patients according to demographic data

	N=102	%
Sex:		
Female	60	58.8%
Male	42	41.2%
Side of lesion:		
Left	42	37.8%
Right	69	62.2%
	Mean ± SD	**Range**
Age (year)	54.54 ± 8.62	35 – 69
Diabetes duration (year)	9.93 ± 2.86	5 – 17

Table 2 OCTA parameters pre and postoperatively among the studied patients

	Preoperative	Postoperative	t	*p*
	Mean ± SD	**Mean ± SD**		
CMT (μm)	420.94 ± 56.12	328.29 ± 50.02	15.628	<0.001**
FAZ area (mm)	0.332 ± 0.066	0.343 ± 0.07	-5.916	<0.001**
SCP fovea VD (%)	22.09 ± 4.18	20.88 ± 3.9	9.755	<0.001**
SCP parafovea VD (%)	41.45 ± 3.4	40.75 ± 3.46	5.902	<0.001**
DCP fovea VD (%)	28.96 ± 3.8	27.49 ± 3.78	10.359	<0.001**
DCP parafovea VD (%)	44.9 ± 2.51	44.47 ± 2.51	4.504	<0.001**
BCVA	0.69 ± 0.16	0.38 ± 0.18	19.751	<0.001**

t paired sample t test **$p \leq 0.001$ is statistically highly significant

level ($p<0.05$). By employing multiple regression analysis, a predictive model pertaining to the variables associated with early treatment response was constructed. Utilizing a weighted least-squares model that was nonlinear, a receiver operator characteristic (ROC) curve was generated. For each observed value, the ROC curve was generated by plotting sensitivity against specificity minus one. By utilizing the area under the ROC curve (AUC), The performance of the parameters used to differentiate eyes that responded to treatment from those that displayed stable or deteriorating conditions was evaluated in comparison.

Results

This study included 111 eyes of 102 participants who having diabetic macular edema (DME). The 102 participants were 58.8% (60) females and 41.2% (42) males. Mean age was 54.54±8.62 years (range: 35 to 69 years), the mean DM duration was 9.93±2.86 years (range: 5–17), the 111 eyes were 69 (62.2%) right and 42 (37.8%) left (Table 1).

A postoperative reduction in CMT was observed to be statistically significant, dropping from 420.94±56.12 to 328.29±50.02. A statistically significant change in BCVA is observed between preoperative and postoperative measures (0.69±0.16 to 0.38±0.18) (Table 2) concerning response, about 76 eyes (68.5%) had good response while 35 eyes (31.5%) had poor response.

Table 3 Comparison between the studied groups regarding BCVA pre and postoperatively

	Good response	Poor response	t	*P*
	Mean ± SD	**Mean ± SD**		
BCVA				
Preoperative	0.704 ± 0.158	0.661 ± 0.164	1.302	0.196
Postoperative	0.305 ± 0.131	0.54 ± 0.178	-6.965	<0.001**
p	<0.001**	<0.001**		
	Median (IQR)	**Median (IQR)**	**Z**	**P**
Change in BCVA	-0.42(-0.48, -0.3)	-0.12(-0.18, 0)	-8.809	<0.001**

χ^2Chi square test t independent sample t test Z Mann Whitney test **$p \leq 0.001$ is statistically highly significant

A statistically significant relation between response and postoperative BCVA is observed. There was significant change in BCVA postoperatively as compared to preoperative value. A significant relation was observed between response and postoperative change in BCVA ($P<0.001$ for both variables) (Table 3).

By comparing the pre injection size of the foveal avascular zone area (FAZ-A) in both groups, it found that the mean±SD of FAZ-A was 0.297±0.038 mm in good responder patients compared to 0.407±0.05 mm in non-responder patients. The preoperative SCP foveal vascular density (VD) was 24.02±3.01% in good responder patients versus 17.89±3.19% um in poor responders. The preoperative SCP parafoveal VD was 43.06±2.67% in good responder patients versus 37.96±1.82% um in poor responders. The preoperative DCP foveal VD was 30.58±2.89% in good responder patients versus 25.45±3.14% in poor responders. The preoperative DCP parafoveal VD was 45.66±2.21% in good responder patients versus 43.26±2.35% um in poor responders; a statistically significant relation between response and all of FAZ area, SCP foveal VD, SCP parafoveal VD, DCP foveal VD, DCP parafoveal VD preoperatively ($P<0.001$ for each) was observed (Table 4).

The best cutoff of preoperative SCP foveal VD in prediction of good response is ≥21.05% with area under curve 0.913 (95% CI; 0.859 to 0.967), at which sensitivity is 80.3% and specificity 80% ($p<0.001$). The best cutoff of preoperative SCP parafoveal VD in prediction of good response is ≥39.65% with area under curve 0.92 (95% CI; 0.87 to 0.97), at which sensitivity is 85.5% and specificity 82.9% ($p<0.001$) The best cutoff of preoperative DCP foveal VD in prediction of good response is ≥27.5% with area under curve 0.918 (95% CI; 0.865 to 0.97), at which sensitivity is 90.8% and specificity 82.9% ($p<0.001$) The best cutoff of preoperative DCP parafoveal VD in prediction of good response is ≥44.05% with area under curve 0.79 (95% CI; 0.706 to 0.875), at which sensitivity is 77.6% and specificity 74.3% ($p<0.001$) (Table 5, and Fig. 1).

Table 4 Comparison between the studied groups regarding OCTA parameters

	Good response	Poor response	t	*P*
	Mean ± SD	Mean ± SD		
CMT (μm)				
Preoperative	436.22 ± 54.66	387.74 ± 44.05	4.601	<0.001**
Postoperative	308.12 ± 33.09	372.09 ± 52.86	-6.59	<0.001**
p (t)	<0.001**	<0.001**		
FAZ area (μm)				
Preoperative	0.297 ± 0.038	0.407 ± 0.05	-12.805	<0.001**
Postoperative	0.305 ± 0.038	0.426 ± 0.049	-14.124	<0.001**
p (t)	<0.001**	<0.001**		
SCP fovea VD (%)				
Preoperative	24.02 ± 3.01	17.89 ± 3.19	9.78	<0.001**
Postoperative	22.6 ± 2.89	17.15 ± 3.17	8.946	<0.001**
p (t)	<0.001**	0.01*		
SCP parafovea VD (%)				
Preoperative	43.06 ± 2.67	37.96 ± 1.82	11.735	<0.001**
Postoperative	42.35 ± 2.75	37.29 ± 2.0	10.954	<0.001**
p (t)	<0.001**	<0.001**		
DCP fovea VD (%)				
Preoperative	30.58 ± 2.89	25.45 ± 3.14	8.462	<0.001**
Postoperative	29.03 ± 2.88	24.15 ± 3.36	7.856	<0.001**
p (t)	<0.001**	<0.001**		
DCP parafovea VD (%)				
Preoperative	45.66 ± 2.21	43.26 ± 2.35	5.211	<0.001**
Postoperative	45.09 ± 2.16	43.12 ± 2.72	4.115	<0.001**
p (t)	<0.001**	0.277		

p (t) p for paired sample t test, t independent sample t test, Z Mann Whitney test
**$p \leq 0.001$ is statistically highly significant

The best cutoff of preoperative FAZ area in prediction of good response is ≤0.3625 mm with area under curve 0.955 (95% CI; 0.913 to 0.966), at which sensitivity is 98.7% and specificity 82.9% ($p < 0.001$) (Table 6, and Fig. 1). Cases are illustrated in (Figs. 2 and 3).

Discussion

A prospective interventional study was undertaken utilizing OCTA to determine biomarkers that might serve as predictors of an early anatomical response to IVR injection for DME. An intravitreal OCTA image was obtained of 111 eyes from 102 naïve patients with DME, both prior to and following three IVR injections administered monthly.

It is crucial to comprehend and forecast the response to the employed therapy in order to effectively manage the expectations of both the patient and the provider regarding potential outcomes. In specific instances, this data may prompt an alternative course of treatment or even a different managerial choice regarding the patients in question [7].

The superficial and deep capillary plexuses evaluation in OCTA in conjunction with FAZ-A may provide a more accurate prognosis of treatment response and enable earlier management of DME, according to a number of studies that examined this subject and produced contradictory findings. [12]; Previous studies has demonstrated the potential utility of projection-resolved OCTA in forecasting the initial anatomical reaction of DME to intravitreal bevacizumab therapy. [13]. Hsieh YT, et al. [11] established, at least one year prior to loading ranibizumab treatment, that parafoveal VD in the superficial layer was an independent predictor of visual improvement in eyes with DME. On the other hand Lee J, et al. [14] proved that a poor response's eyes to anti-VEGF treatment exhibited significant impairment in the DCP integrity, but not the SCP, in comparison to DME eyes that exhibited a positive response.

Diverse factors, such as disparate study designs, variations in inclusion criteria and patient characteristics or approaches to image analysis and vascular density quantification, may have contributed to this dispute [15].

In light of previous study that has solely focused on post-treatment OCTA metrics without considering baseline retinal characteristics in relation to treatment outcomes, our investigation aimed to identify biomarkers by comparing pre-treatment and post-treatment OCTA metrics [14]; The clinical applicability of these findings as biomarkers was thus restricted.

In the same way of our findings, Durbin et al. [16] provided evidence that the correlation between VA and VD in the superficial layer of DR was not evident in the deep layer. Flow projection artifacts arise due to the reflection of faint shadows caused by superficial blood flow onto more profound retinal layers. As a consequence, the vascular patterns originating from the deeper layers

Table 5 Performance of preoperative parameters in prediction of good response among studied patients

parameter	Cutoff	AUC	95% CI	Sensitivity	Specificity	*P*
SCP fovea	≥21.05	0.913	0.859 – 0.967	80.3%	80%	<0.001**
SCP para	≥39.65	0.92	0.87 – 0.97	85.5%	82.9%	<0.001**
DCP fovea	≥27.5	0.918	0.865 – 0.97	90.8%	82.9%	<0.001**
DCP para	≥44.05	0.79	0.706 – 0.875	77.6%	74.3%	<0.001**

AUC area under curve CI confidence interval **$p \leq 0.001$ is statistically highly significant

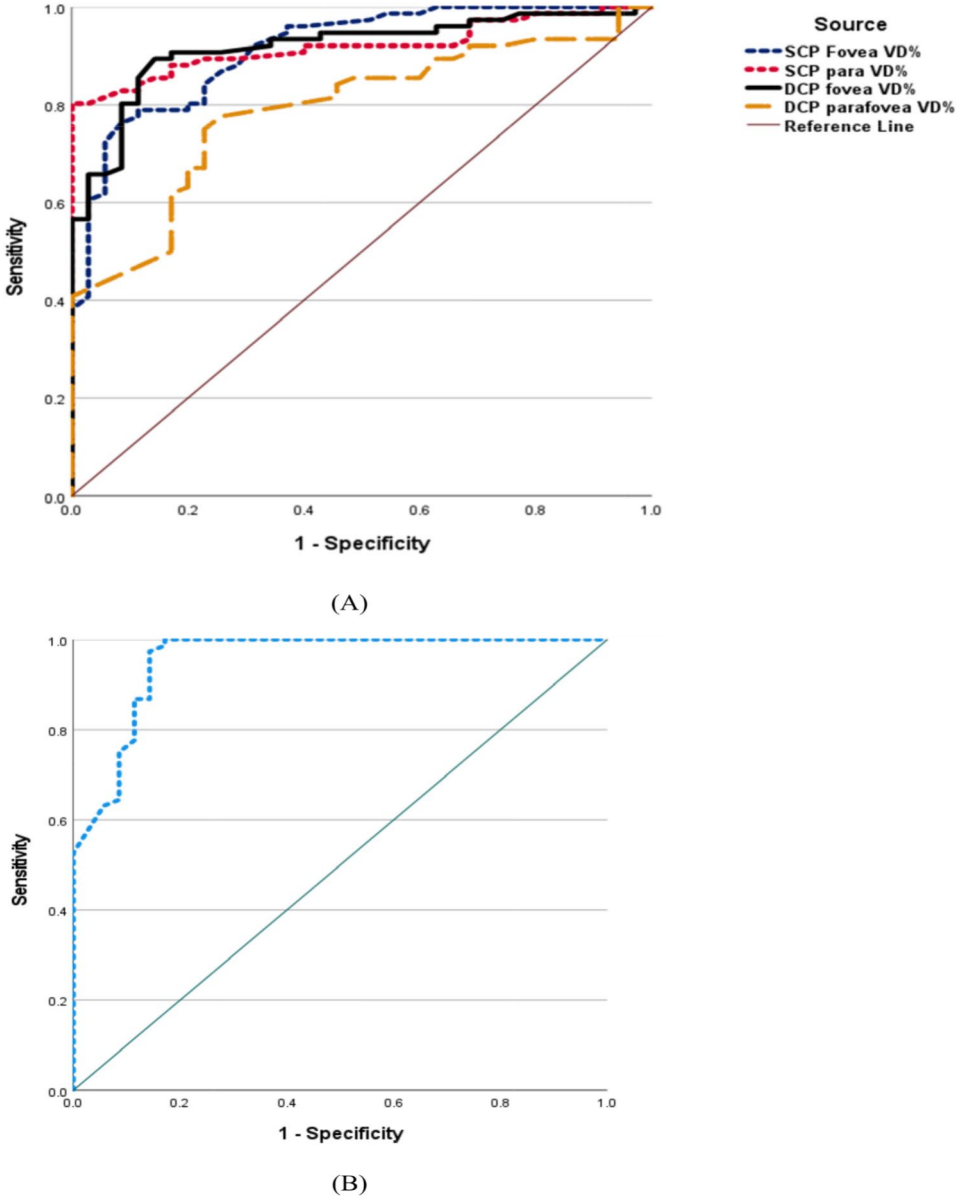

Fig. 1 ROC curves showing (**A**): performance of preoperative DCP and SCP fovea and parafovea in prediction of good response among studied patients, (**B**): performance of preoperative FAZ in prediction of good response among studied patients

Table 6 Performance of preoperative FAZ in prediction of good response among studied patients

Cutoff	AUC	95% CI	Sensitivity	Specificity	*P*
≤0.3625	0.955	0.913 – 0.966	98.7%	82.9%	<0.001**

AUC area under curve CI confidence interval **$p \leq 0.001$ is statistically highly significant

are replicated in the superficial plexuses. Consequently, acquiring an unobstructed image of the deeper vascular plexuses becomes unattainable in the absence of software designed to eliminate projection artifacts. [17] By eliminating projection artifacts, we were able to more precisely characterize these retinal vascular layers in order to predict treatment response in our study.

However, Lee J, et al. [14] utilized software that failed to eliminate projection artifacts, a factor that could have significantly impacted DCP measurements.

The SCP's initial parafoveal VD predicted visual improvement, in contrast to the findings of alternative investigations which failed to establish a correlation between initial OCTA metrics and anatomical improvement [11] which is comparable to the results in our trail.

Previous study has established that the FAZ size is more distinct on OCTA than on alternative imaging modalities like FA [10] associates with visual improvement with anti-VEGF treatment [18] Contradictory findings have been reported in other studies that utilized

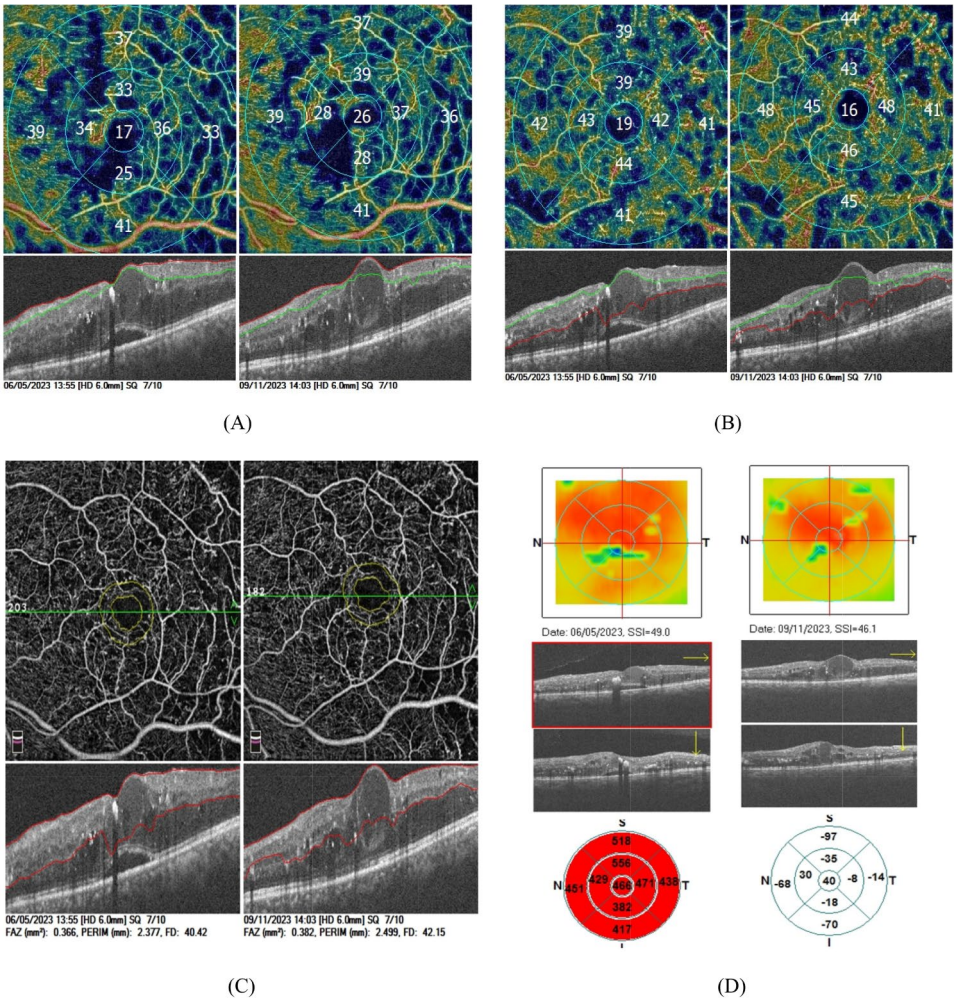

Fig. 2 Case 1 (poor responder): (**A**): SCP pre and post treatment with non-resolved DME, (**B**): DCP pre and post treatment with non-resolved DME, (**C**): FAZ-A pre and post treatment with non-resolved DME, (**D**): OCT pre and post treatment with non-resolved DME

OCTA to assess the impact of intravitreal injections of anti-VEGF agents on the size of the FAZ and VD measurements in the macula of patients with DME; however, these investigations failed to conduct a distinct comparison of changes in responders and non-responders.

An advantageous aspect of our study is that we enrolled naïve eyes that had not undergone any previous treatments that may have caused iatrogenic vision loss. This includes vision loss caused by the progressive deterioration of retinal function or long-term growth factor suppression associated with anti-VEGF agents.

According to the results of our study, OCTA characteristics may serve as a predictor of an early anatomical response in treatment naïve eyes undergoing IVR for DME. Eyes whose CMT decreases following three IVB injections experience enhanced visual acuity, in contrast to those whose condition does not improve or worsens despite treatment. This finding aligns with numerous prior studies, as. Elnahry G.A. et al. [13] and Hsieh YT, et al. [11]

Our study's findings suggest that clinicians may search for alternative anti-VEGF agents, intravitreal steroids, or focal laser treatment if they are able to identify eyes that are unlikely to respond to IVR. The results of our study suggest that eyes with large FAZ-A and or insufficient baseline VD measurements, particularly at the SCP level, demonstrated a reduced anatomical response corresponding to that of eyes that responded initially to three initial IVR injections. This suggested that eyes lacking response to IVR may be more susceptible to developing macular ischemia. This may occur as a result of increased VEGF production, which could render anti-VEGF treatment ineffective and allow DME to persist [19].

The inclusion of patients in varying stages of DR and the three-month follow-up period, which is insufficient for evaluating eyes with a delayed response to treatment, are both limitations of our research.

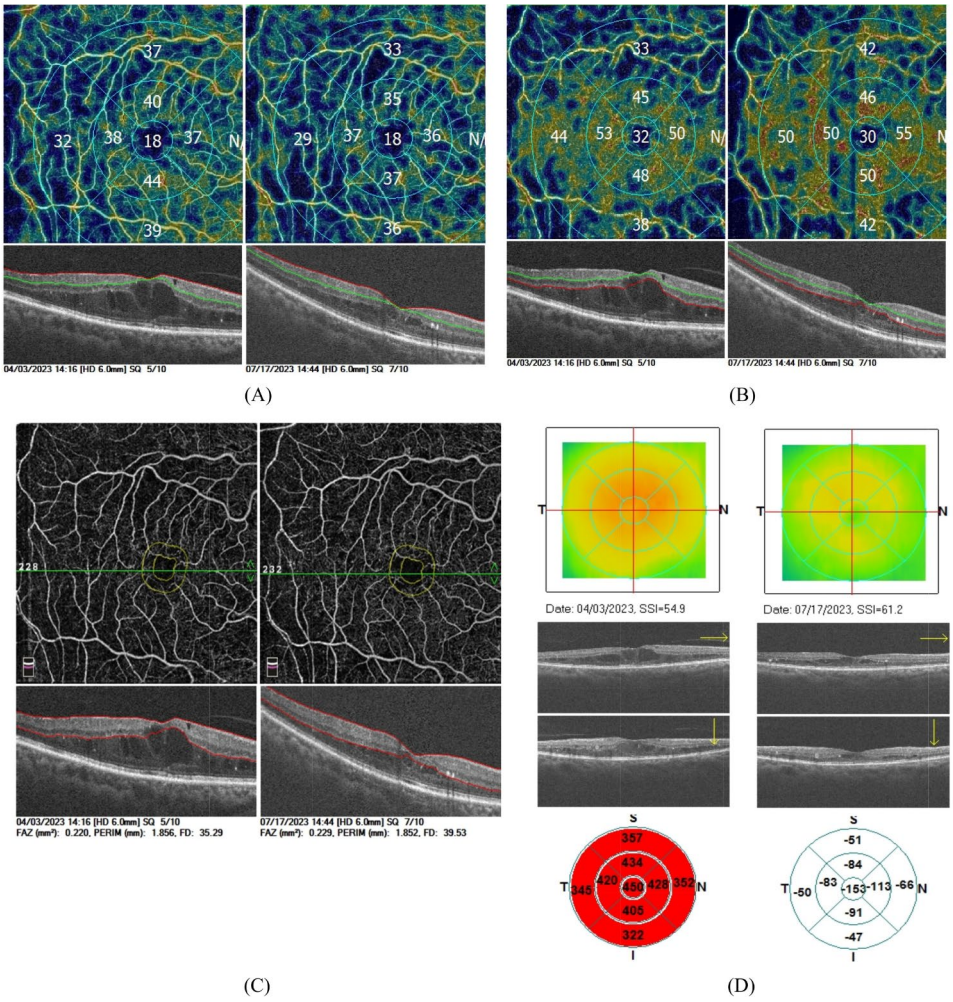

Fig. 3 Case 2 (good responder): (**A**): SCP pre and post treatment with non-resolved DME, (**B**): DCP pre and post treatment with non-resolved DME, (**C**): FAZ-A pre and post treatment with non-resolved DME, (**D**): OCT pre and post treatment with non-resolved DME

Conclusion

OCTA plays a potential role for providing insight and predictability in the management of DME demonstrating an early anatomical response to IVR. The VD in the superficial and deep capillary plexuses at the macula level, as well as FAZ-A size, at baseline can predict an early-treatment response to IVR; supporting the belief that eyes with more severe ischemia detected by OCTA at baseline are less responsive to anti-VEGF treatment. Larger studies, rather with longer follow-up periods, are needed to clarify the relationship between the numerous OCTA-derived vascular parameters and the response of eyes with DME to treatment. Future advances in OCTA scanning technology may increase the ability to predict treatment outcome based on vascular features.

Acknowledgements
Not applicable.

Author contributions
Ahmed Basiony, Hatem Marey, Ahmed Ezat and Marwa Zaky shared Concepts, Design, Definition of intellectual content, Literature search, Clinical studies, Data acquisition and Manuscript editing in this study. Ahmed Ezat did Data analysis, Statistical analysis and Manuscript preparation.Ahmed Basiony did Manuscript reviewing.

Funding
Open access funding provided by The Science, Technology & Innovation Funding Authority (STDF) in cooperation with The Egyptian Knowledge Bank (EKB). No funding was received.

Data availability
The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by Ethical Committee of the Menoufia University Hospital, all patients received a thorough explanation of the study design and aims followed by a signed informed consent. The study was conducted in compliance with the tenets of the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 22 February 2024 / Accepted: 24 June 2024
Published online: 01 October 2024

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