Research Square

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Changes in retinal and choroidal thickness and blood flow after anti-VEGF therapy for diabetic macular edema: a retrospective study

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Abstract

Purpose: To clarify the role of anti-VEGF therapy in diabetic macular edema, we measured retinal and choroidal thickness and perfusion indices with the use of optical coherence tomography angiography(OCTA).

Methods: Retrospective clinical study. A total of 45 patients (45 eyes) with DME at the Affiliated Eye Hospital of Chengdu University of Traditional Chinese Medicine from January 2023 to January 2026 were enrolled. All patients received three consecutive monthly intravitreal injections of conbercept. OCTA examinations were performed at baseline, 1 month, and 3 months after the first injection to measure central macular thickness (CMT), subfoveal choroidal thickness (SFCT), vessel density of the superficial capillary plexus (SCP) and deep capillary plexus (DCP), foveal avascular zone (FAZ) area, and parafoveal vessel density at 300 μm (FD-300). Best-corrected visual acuity (BCVA) was also recorded. The changes in these parameters before and after treatment were compared.

Results: The study included 45 patients (45 eyes), comprising 21 male patients (21 eyes) and 24 female patients (24 eyes),with a mean age of (54.44±12.09) years. The mean duration of diabetes was (13.33 ± 4.36) years, and the baseline glycated hemoglobin (HbA1c) level was (7.36% ± 1.72)%.At the last follow-up, BCVA significantly improved ($P < 0.001$), CMT significantly decreased with amelioration of macular edema ($P < 0.05$), SFCT significantly decreased ($P < 0.05$), and microcirculation in the foveal SCP and DCP significantly improved compared with baseline ($P < 0.05$). No statistically significant differences were observed in the remaining parameters ($P > 0.05$).

Conclusion: The study demonstrated that anti-VEGF therapy effectively reduced retinal thickness in eyes with DME, alleviated macular edema, inhibited neovascularization, decreased exudation and hemorrhage, preserved retinal function, and improved visual acuity, thereby enhancing patients' quality of life.

1. Background

Diabetic retinopathy (DR) is a vision-threatening retinal vascular disease associated with sustained hyperglycemia, and is one of the more common and severe microvascular complications of diabetes [1]. As DR progresses, macular vascular lesions worsen, leading to fluid leakage and the development of diabetic macular edema (DME).DME is one of the main causes of central vision loss in patients with DR. Its development is closely linked to disruption of the blood-retinal barrier, increased vascular permeability, and inflammatory responses, and it can occur at any stage of the disease [2]. DME causes retinal thickening and edema, resulting in vision loss and metamorphopsia.Currently, the treatment of DME mainly includes intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents, retinal laser photocoagulation, corticosteroid therapy, and combination therapy [3]. Numerous clinical studies have confirmed that intravitreal anti-VEGF injection can effectively alleviate macular edema, inhibit neovascularization, reduce exudation and hemorrhage, preserve retinal function, and improve visual acuity, thereby enhancing patients’ quality of life, making it the first-line treatment for DME [4].

However, the long-term effects of anti-VEGF therapy on the retinal and choroidal microcirculation in eyes with DME remain to be fully elucidated.

As a non-invasive imaging modality, optical coherence tomography angiography (OCTA) has been increasingly utilized to delineate the microvascular networks within the retina and choroid. By acquiring high-speed sequential cross-sectional scans and applying motion contrast or phase-based algorithms, OCTA enables three-dimensional reconstruction of the vasculature [5] and provides quantitative metrics of vessel density and morphology in individual retinal and choroidal layers [6]. While previous investigations have applied OCTA to track retinal thickness alterations after anti-VEGF treatment in eyes with diabetic macular edema (DME) [7], the concurrent dynamic responses of retinal and choroidal thickness together with blood perfusion following therapy remain incompletely characterized. Accordingly, we conducted a retrospective analysis of DME patients who received anti-VEGF therapy at our institution and employed wide-field OCTA to quantitatively evaluate the therapeutic effects on retinal and choroidal thickness as well as perfusion, aiming to inform clinical efficacy assessment.

2. Methods

2.1.Design and participants

Retrospective study. A total of 45 patients (45 eyes) with DME who received anti-VEGF therapy at the Affiliated Eye Hospital of Chengdu University of Traditional Chinese Medicine between January 2023 and January 2026 were enrolled. Among them, 21 were male (21 eyes) and 24 were female (24 eyes). The mean age was 54.44 ± 12.09 years, and the mean duration of diabetes was 13.33 ± 4.36 years,and baseline glycated hemoglobin (HbA1c) was 7.36%±1.72%. (As seen in Table 1)

Inclusion criteria[8]: (1) a confirmed diagnosis of type 2 diabetes, the presence of DME involving the fovea as verified by fundus examination and OCT, and central macular thickness (CMT) ≥ 300 μm.(2) Received three consecutive monthly intravitreal injections of conbercept (0.5 mg/0.05 mL).(3) Patients must consent to a specified follow-up period to evaluate the surgical outcomes and long-term effects.

Exclusion criteria: (1) Prior vitrectomy, macular laser treatment, or anti-VEGF therapy;(2) Concomitant proliferative diabetic retinopathy, retinal vein occlusion, uveitis, glaucoma, or other macular diseases;(3) Significant media opacity that markedly compromises OCTA image quality;(4) Ocular infection or recent ocular surgery.This study was approved by the Medical Ethics Committee of the Affiliated Eye Hospital of Chengdu University of Traditional Chinese Medicine (Approval No. 2022yh-007), and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Table 1
Preoperative data of the patients who underwent anti-VEGF for DME

Characteristics	Values
No.of eyes/no.of patients	45/45
Ages	54.44 ± 12.09
Sex(M/F)	21/24
Duration of diabetes (years)	13.33 ± 4.36
HbA1c (%)	7.36%±1.73%
Data are mean ± standard deviation unless otherwise indicated	
M,male;F,female;HbA1c,Glycated hemoglobin	

2.2. Primary Indicators Measurement Methods

Best-corrected visual acuity (BCVA) was obtained using an international standard logarithmic chart. The results were converted to the logarithm of the minimum angle of resolution (LogMAR) prior to statistical analysis. Intraocular pressure (IOP) was measured using a non-contact tonometer.OCTA scans were performed with the BM-400K BMizar device (TowardPi Medical Technology, Beijing, China). The Macula Angio scanning protocol was selected, centered on the fovea, with a 6 mm×6 mm scan area. The built-in blood flow analysis software was used to analyze the average blood flow density in the foveal area and the inner ring (superior, inferior, nasal, and temporal quadrants). Automated segmentation algorithms generated blood flow density images of the superficial capillary plexus (SCP, from the internal limiting membrane to 9μm below the inner plexiform layer) and the deep capillary plexus (DCP, from 9μm below the inner plexiform layer to the outer plexiform layer). Blood flow density was defined as the percentage of vascular pixels relative to the total pixels in the scanned region, expressed as a percentage. The foveal avascular zone (FAZ) area (mm^2), the parafoveal 300 μm blood flow density (%), and the central macular thickness (CMT, μm) were also obtained. Choroidal thickness was measured using the enhanced depth imaging (EDI) mode, and subfoveal choroidal thickness (SFCT, μm) was defined as the perpendicular distance from the outer border of the hyperreflective line of the retinal pigment epithelium to the inner border of the sclera. With the combination of a long wavelength(1060nm)full range swept source and a 400 kHz A-scan rate, With the high scan rate and an eye tracking rate of 128 Hz, it shortened acquisition time, reduced imaging artefacts and eliminated interference caused by eye motion and blinks.The axial resolution was 3.8μm and the transverse resolution was 10μm.The TowardPi OCTA allowed for the in vivo visualization of three-dimensional (3-D) vascular networks in the retina and choroid.The OCTA images were acquired by the TowardPi 3-D spatial identification algorithm.The retinal vessels and choriocapillaris were identified by higher-order moments decorrelation algorithm.The medium- and large-sized choroid vessels from Sattler’s layer and Haller’s layer were visualized by 3-D Threshold Segmentation Algorithm.The images were free of obvious motion or projection artifacts. The

segmentation boundaries of the SCP and DCP were automatically identified by the software and subsequently verified and manually corrected by the operator. All measurements were performed by the same experienced technician.Details are shown in Fig. 1.

This case presents a 62-year-old male patient with DME in the right eye and a 12-year duration of diabetes. Preoperative best-corrected visual acuity BCVA(logMAR) was 0.52, which improved to 0.40 at the last postoperative follow-up. (A) Preoperative foveal retinal thickness map. (B) Foveal retinal thickness map at the 1-month postoperative follow-up. Different colors indicate different foveal retinal thicknesses.

2.3 Surgical Method

(1) Preoperative preparation:For 3 consecutive days before surgery, ofloxacin eye drops (National Drug Approval Number: H200113438; 5 mL:15 mg) were instilled into the surgical eye four times daily. Strict disinfection of the eye was performed prior to the procedure. After topical anesthesia, povidone-iodine solution [National Drug Approval Number: H51022887; 500 g (10%)] was instilled into the conjunctival sac (avoiding the cornea), retained for 3 minutes, and then irrigated.(2) Surgical procedure:A needle was inserted perpendicularly into the vitreous cavity at a point 3.5–4.0 mm posterior to the superotemporal limbus, and conbercept ophthalmic injection [National Drug Approval Number: S20130012; 0.5 mg/0.05 mL] was administered intravitreally at a dose of 0.05 mL per injection. Injections were performed once monthly for a total of three injections. No adjunctive laser photocoagulation or other medications were used during the treatment period.(3) Postoperative management:Tobramycin and dexamethasone ophthalmic ointment (National Drug Approval Number: HJ20020496; 3 g per tube, containing tobramycin 9 mg and dexamethasone 3 mg) was applied to the eye, and a sterile gauze pad was placed over the operated eye.

2.4. Postoperative Follow-up

Patients who completed follow-up visits at 1 month and 3 months postoperatively were enrolled. Changes in BCVA(logMAR), CMT, SFCT, SCP, DCP, FAZand other relevant parameters were recorded to evaluate the effects of anti-VEGF therapy on retinal structure and function in patients with DME.

2.5.Statistical analysis

Statistical analysis was performed using SPSS 26.0 software. For continuous variables, the Shapiro–Wilk test was used to assess normality, and Levene's test was used to assess homogeneity of variances.

Data are expressed as mean±standard deviation ($\bar{x}\pm s$). Repeated measures analysis of variance (RMANOVA) with Bonferroni post-hoc tests was applied to evaluate differences in BCVA(logMAR), CMT, SFCT, SCP, DCP, FAZ, and other relevant parameters before anti-VEGF therapy and at 1 month and 3 months postoperatively. For non-normally distributed data, the Wilcoxon non-parametric test was used. A two-sided P value < 0.05 was considered statistically significant.

3. Results

3.1 Evolution of BCVA、CMT、SFCT

The baseline best-corrected visual acuity BCVA(logMAR) was (0.65 ± 0.45). At 1 and 3 months after treatment, the mean BCVA(logMAR) improved to (0.46 ± 0.37) and (0.33 ± 0.27), respectively, with a significant difference compared with baseline (P < 0.001). The baseline central macular thickness CMT was (392.02 ± 139.90) μm, and the mean CMT significantly decreased to (338.91 ± 140.32) μm at 1 month and (322.26 ± 85.60) μm at 3 months post-treatment (P < 0.05). The subfoveal choroidal thickness SFCT at baseline, 1 month, and 3 months after treatment was (260.51 ± 106.16) μm, (250.02 ± 96.19) μm, and (243.80 ± 91.15) μm, respectively,with a significant difference compared with baseline (P < 0.05). Above results are given in Table 2 and Fig. 2.

Table 2
Measurements(mean±standard deviation) of BCVA、CMT 、SFCT between preoperative and postoperative examinations

Characteristics	Preoperative	1 month after surgery	3 months after surgery	P value [a]
BCVA(logMAR)	0.65 ± 0.45	0.46 ± 0.37	0.33 ± 0.27	0.001
CMT(μm)	392.02 ± 139.90	338.91 ± 140.32	322.26 ± 85.60	0.006
SFCT(μm)	260.51 ± 106.16	250.02 ± 96.19	243.80 ± 91.15	0.037

BCVA,Best corrected vision acuity;CMT,Central Macular Thickness;SFCT,Subfoveal Choroidal Thickness;

P value [a] RMANOVA

3.2 Retinal blood flow

The retinal blood flow results at baseline and at 1 and 3 months postoperatively are presented in Table 3. At baseline, the foveal superficial retinal blood flow was (26.88 ± 6.71). At 1 and 3 months after surgery, the superficial retinal blood flow was (27.94 ± 7.05) and (29.94 ± 7.32), respectively, which were significantly different from the pretreatment value (P < 0.05). However, no statistically significant differences were observed in the inner ring (superior, inferior, nasal, and temporal quadrants) compared with pretreatment (P > 0.05). The preoperative foveal deep retinal blood flow was (30.02 ± 6.46), and at 1 and 3 months postoperatively, it was (31.74 ± 6.77) and (33.54 ± 6.74), respectively, which were significantly different from the pretreatment value (P < 0.05). However, no statistically significant differences were observed in the inner ring (superior, inferior, nasal, and temporal quadrants) compared with pretreatment (P > 0.05),as shown in Table 4.

Table 3
Measurements(mean±standard deviation) of SCP between preoperative and postoperative examinations

SCP	Subfoveal	Superior	Inferior	Nasal	Temporal
Preoperative	26.88 ± 6.71	35.25 ± 5.95	36.34 ± 6.49	36.34 ± 6.49	34.28 ± 7.74
1 month after surgery	27.94 ± 7.05	36.45 ± 6.31	37.85 ± 5.29	36.42 ± 6.22	34.71 ± 8.09
3 months after surgery	29.94 ± 7.32	37.94 ± 6.85	38.62 ± 8.40	37.20 ± 5.41	37.48 ± 6.34
P value [a]	0.041	0.133	0.263	0.321	0.056

Table 4 Measurements(mean±standard deviation) of DCP between preoperative and postoperative examinations

DCP	Subfoveal	Superior	Inferior	Nasal	Temporal
Preoperative	30.02±6.46	41.29±5.84	42.28±4.24	42.45±3.68	42.57±4.40
1 month after surgery	31.74±6.77	41.34±5.84	42.68±4.03	42.77±4.01	42.25±4.50
3 months after surgery	33.54±6.74	42.24±5.85	42.65±4.12	43.05±4.36	42.91±4.37
P value [a]	0.043	0.370	0.310	0.396	0.357

SCP,Superficial retinal capillary plexus density;DCP,Deep retinal capillary plexus density;

P value [a] RMANOVA

3.3 Evolution of FAZ

The FAZ area was (0.346 ± 0.152) mm² at baseline, (0.341 ± 0.136) mm² at 1 month post-treatment, and (0.342 ± 0.149) mm² at 3 months post-treatment. The parafoveal blood flow density within the 300 μm region was (34.58 ± 6.69) % at baseline, (34.03 ± 5.95) % at 1 month postoperatively, and (34.11 ± 6.63) % at 3 months postoperatively. Neither parameter showed a significant difference (P > 0.05).Above results are given in Table 5 and Fig. 3.

Table 5
Measurements(mean±standard deviation) of FAZ、FD-300 of Subfoveal between preoperative and postoperative examinations

Characteristics	Preoperative	1 month after surgery	3 months after surgery	P value [a]
FAZ(mm²)	0.346 ± 0.152	0.341 ± 0.136	0.342 ± 0.149	0.958
FD-300(%)	34.58 ± 6.69	34.03 ± 5.95	34.11 ± 6.63	0.780
FAZ,Foveal Avascular Zone;FD-300,Foveal Density − 300 μm				

3.4 Adverse Reactions

No severe complications, including endophthalmitis, retinal detachment, persistent ocular hypertension, or cataract progression, occurred following any injection. Eight patients experienced transient intraocular pressure elevation (< 25 mmHg) after injection, which resolved spontaneously within 3 days. Subconjunctival hemorrhage was observed in 7 patients and resolved within 1 week.

4. Discussion

This study utilized the OCTA system to evaluate the effects of anti-VEGF therapy on retinal and choroidal thickness and blood perfusion in patients with DME. The results demonstrated that after three consecutive monthly intravitreal injections of conbercept, CMT was significantly reduced and BCVA was significantly improved, with notable improvement observed as early as 1 month after treatment and further stabilization achieved at 3 months. This finding is consistent with the studies by Zhou et al. [9, 10]. The effect of anti-VEGF therapy on SFCT was also largely consistent with the existing study by Shi et al. [11], which reported a progressive reduction in SFCT following conbercept injection. Conbercept is a multi-target recombinant fusion protein anti-VEGF agent that specifically binds to VEGF, blocks its interaction with receptors, and inhibits the activation of downstream signaling pathways [12, 13], thereby reducing vascular endothelial cell permeability and abnormal proliferative activity, decreasing vascular leakage, promoting the resolution of macular edema, contributing to the restoration of normal retinal layer architecture, and improving visual function [14, 15]. CMT is a core morphological parameter reflecting the severity of macular edema, and its reduction generally indicates partial recovery of the blood–retinal barrier function and effective absorption of interstitial fluid [16, 17]. Moreover, in this study, the extent of retinal edema resolution was temporally correlated with visual improvement, suggesting a close relationship between morphological recovery and functional prognosis.

OCTA enables noninvasive, high-resolution visualization of the macular microcirculation [18]. This study found that, compared with pretreatment values, the microcirculation of the SCP and DCP in the fovea improved at 1 month and 3 months after treatment, with statistical significance. This finding is consistent with the results of Sheng et al. [19], which included 80 DME patients (122 eyes) and demonstrated that the differences in vessel density of the superficial and deep foveal capillary plexuses before and after anti-VEGF therapy were statistically significant (all $P < 0.05$). However, some studies have shown that anti-VEGF therapy has a relatively limited effect on vessel density. The study by Ma et al. [20] showed that the differences in superficial and deep retinal capillary plexus vessel density after conbercept injection were not statistically significant compared with pretreatment values ($P > 0.05$). This discrepancy may be related to the specific measurement area and the temporal differences in vascular remodeling after edema resolution. Furthermore, our results showed that neither the FAZ area nor FD-300 exhibited statistically significant changes ($P > 0.05$). This negative result is consistent with the observations of Mirshahi et al. [21]; regarding changes in FAZ area, most studies consider that anti-VEGF therapy has no significant effect on it. In DME patients, although macular edema was markedly reduced

1 month after anti-VEGF therapy, blood flow in the foveal avascular zone did not recover synchronously. This may be because, although anti-VEGF can reduce retinal edema and lower CMT, the recovery of retinal microcirculation in ischemic areas requires a longer time; therefore, peripheral vessel density does not change significantly in the short term. In addition, Couturier et al. also reported a similar conclusion [22], that anti-VEGF therapy primarily targets vascular leakage rather than pre-existing non-perfusion areas. In areas with pre-existing capillary loss, anti-VEGF therapy alone is unlikely to restore blood perfusion in the short term. Notably, some studies [23, 24] have found a reduction in FAZ area after anti-VEGF therapy, which may be attributed to milder baseline ischemia, longer follow-up duration, or differences in OCTA devices and algorithms. Therefore, the heterogeneity among different studies suggests that caution is needed when interpreting changes in OCTA parameters.

In summary, this study systematically analyzed the changes in retinal and choroidal thickness and blood flow after anti-VEGF therapy based on OCTA technology and investigated the effects of conbercept on the fundus structure and function in patients with DME. The results demonstrated that intravitreal injection of anti-VEGF effectively reduced retinal thickness, alleviated macular edema, inhibited neovascularization, decreased exudation and hemorrhage, preserved retinal function, improved visual acuity, and enhanced the quality of life in DME patients, with a favorable safety profile [25]. However, this study has certain limitations, including its retrospective design, relatively small sample size, and a follow-up period of only 3 months. Future prospective, large-sample, multicenter studies with longer follow-up durations are warranted to further validate our findings and to explore the time window of microcirculatory recovery and its relationship with long-term prognosis.

Abbreviations

Abbreviation	English Full Term
DME	Diabetic Macular Edema
VEGF	Vascular Endothelial Growth Factor
OCTA	Optical Coherence Tomography Angiography
CMT	Central Foveal Thickness
SFCT	Subfoveal Choroidal Thickness
SCP	Superficial Capillary Plexus
DCP	Deep Capillary Plexus
FAZ	Foveal Avascular Zone
FD-300	Foveal Density within 300 μm
BCVA	Best Corrected Visual Acuity
LogMAR	Logarithm of the Minimum Angle of Resolution
DR	Diabetic Retinopathy

Declarations

CRediT authorship contribution statement

Yongqi Mao: Conceptualization, Methodology, Formal analysis, Writing - Original Draft, Software **Fuwen Zhang:**Resources **Xuan Han:** Data curation **Chuning Wang:** Data curation **Yunhua Tang:** Data curation **Hejiang Ye:** Project administration, Funding acquisition

Declaration of competing interest

The authors declare no conflict of interest.

Consent for publication

Not applicable.

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Data Availability

The Ungdata surveys that support the findings of this study are available from Eye Health with Traditional Chinese Medicine Key Laboratory of Sichuan Province, but restrictions apply to the availability of these data, which were used under licence for the current study and so are not publicly available. The data are, however, available upon request and with the permission of Eye Health with Traditional Chinese Medicine Key Laboratory of Sichuan Province.

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Figures

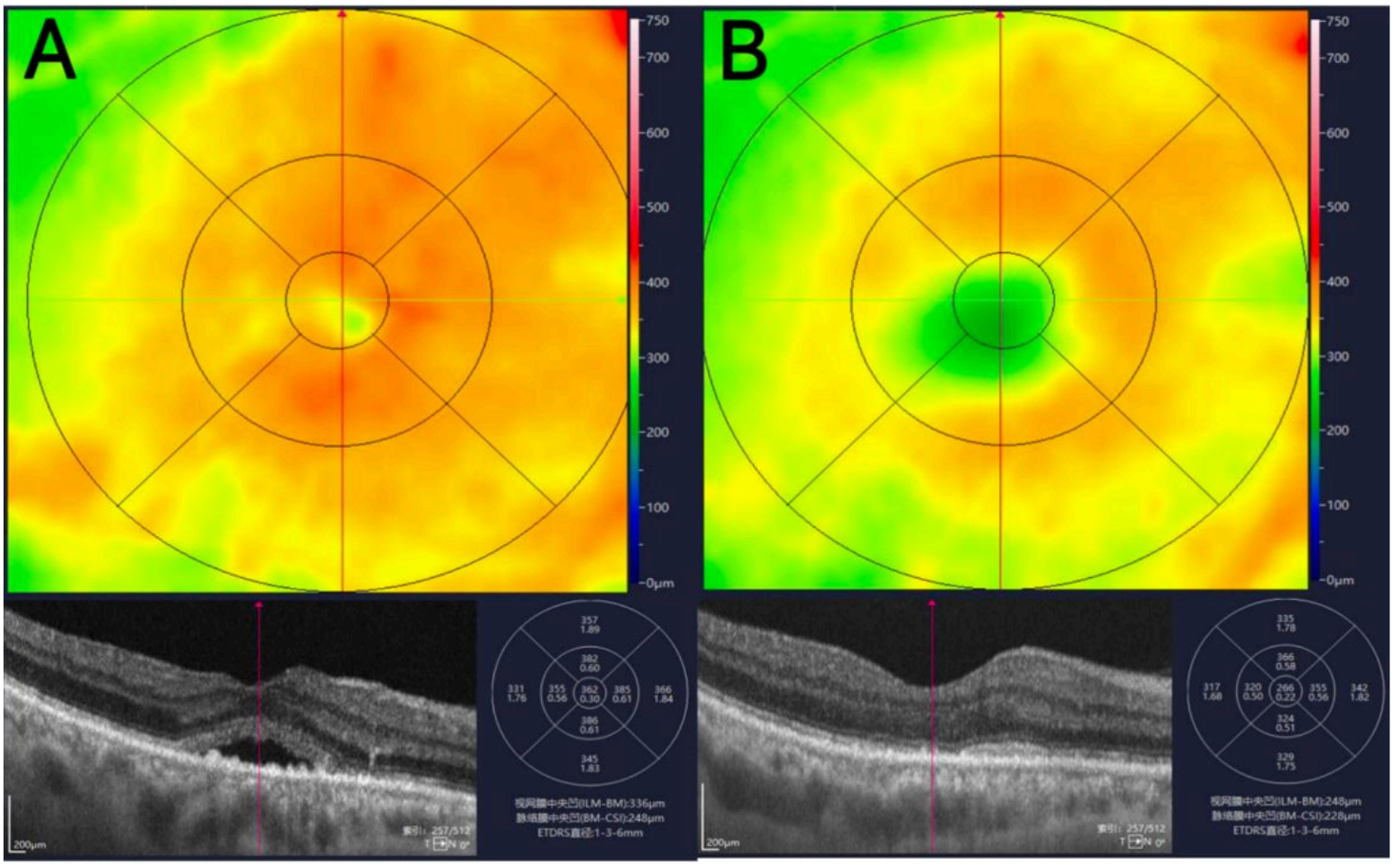


Figure 1

Schematic diagram of foveal retinal thickness analysis.

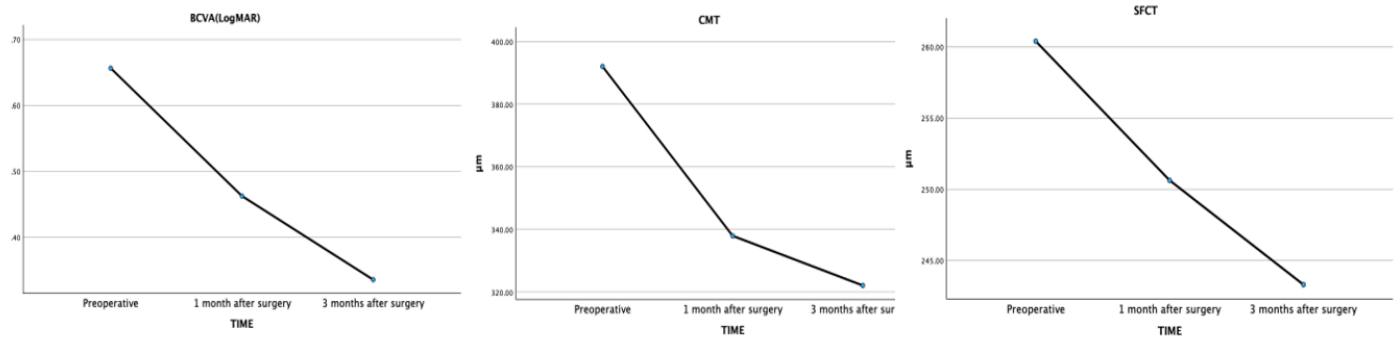


Figure 2

CVA、CMT、SFCT Visualized Line Chart

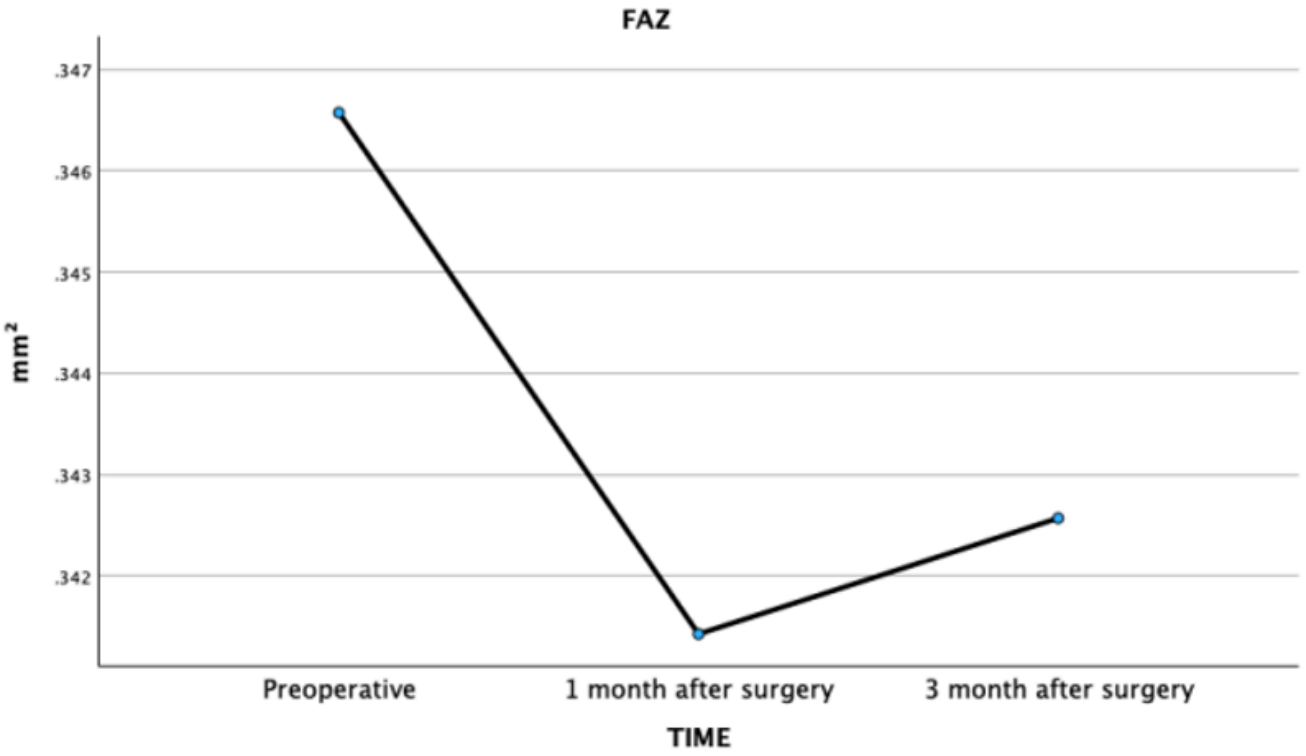


Figure 3

FAZ Visualized Line Chart