OPEN ACCESS Freely available online

Journal of Clinical & Experimental Ophthalmology

Research Article

Structural and Perfusional Findings in Surgically Resolved Myopic Foveoretinal Detachment Eyes and those in Early Stages of Myopic Traction Maculopathy

Miguel A. Quiroz-Reyes[1,2*], Erick A. Quiroz-Gonzalez[1], Jorge Morales-Navarro[1], Miguel A. Quiroz-Gonzalez[2], Boris Moreno-Andrade[1], Mario Carranza-Casas[1], Ana L. Diazceballos-Garcia[1], Alejandra Nieto-Jordan[1], Virgilio Lima-Gomez[3], Federico Graue-Wiechers[1]

[1]Institute of Ophthalmology. Conde de Valenciana Foundation, Mexico City, Mexico; [2]Retina Specialists at the American British Cowdray Hospital, Mexico City, Mexico; [3]Public Assistance Institution, Juarez Hospital, Mexico City, Mexico

ABSTRACT

Purpose: To compare quantitative changes in macular perfusion in normal eyes, healthy highly myopic eyes, non-operated eyes with Myopic Foveoschisis (MF)/Foveoretinal Detachment (FRD), and operated eyes with early stages of Macular Traction Maculopathy (MTM) and fully resolved myopic FRD.

Methods: This retrospective, consecutive, comparative, interventional, single-surgeon, multicentric, case–control study was conducted in 118 eyes (104 individuals) between October 2017 and April 2021. Subjects included normal emmetropic eyes (control emmetropia, n=25), healthy myopic eyes (control high myopia, n=20), non-operated eyes with FRD (non-surgical observational group, n=28), and operated and structurally fully resolved myopic eyes with FRD (surgically treated group, n=45). Long-term postoperative structural, functional and perfusional follow-up evaluations were performed using Spectral Domain Optical Coherence Tomography (SD-OCT) and OCT angiography. The primary outcome measures included structural and perfusional macular status across groups.

Results: In the surgical group, the mean evolution time of myopic FRD was 6.2 ± 3.5 months. The mean follow-up time was 23.9 ± 12.1 months. The mean time for the myopic FRD resolution was 5.0 ± 2.1 weeks. The median best-corrected visual acuity in the FRD surgical group improved from 0.90 logarithm of the minimum angle of resolution (logMAR; 0.60-1.00) to 0.30 logMAR (0.09-1.00), which was highly significant ($p<0.0001$). Quantitative Vessel Density (VD) evaluation findings were significantly different among groups ($p<0.001$). The superficial Foveal Avascular Zone (FAZ) area was significantly greater in the non-surgical group ($p<0.0001$). Better final visual acuity results were significantly correlated with less SD-OCT structural postoperative findings and greater VD quantification values ($p<0.05$). Central subfield foveal thickness was significantly greater in the observational group and significantly lesser in the surgery group (both $p<0.05$).

Conclusion: The results showed a high incidence of postoperative microstructural abnormalities on SD-OCT (48.5%) in the surgical group, high incidence of statistically significant VD quantitative deficiencies and FAZ abnormalities, and significant VD improvement in the fully surgically resolved myopic FRD, relative to the nonsurgical group ($p<0.05$).

Keywords: Choriocapillaris flow; Deep vascular plexus; Foveoretinal detachment; High myopia; Myopic foveoschisis; Foveal avascular zone; Myopic macular degeneration; Myopic macular hole; Myopic macular hole associated retinal detachment; Myopic traction maculopathy; Superficial vascular plexus; Vessel density

Abbreviations: BBG: Brilliant Blue G; BCVA: Best-Corrected Visual Acuity; DCRA: Diffuse Chorioretinal Atrophy; DRT: Diffuse Retinal Thinning; DVP: Deep Vascular Plexus; ELM: External Limiting Membrane; ERM: Epiretinal Membranes; EZ: Ellipsoid Zone; FAZ: Foveal Avascular Zone; FRD: Myopic Foveoretinal Detachment; ILM: Internal Limiting Membrane; IS/OS: Internal Segment/Outer Segment; logMAR: logarithm of Minimum Angle of Resolution; MF: Myopic Foveoschisis; MH: Macular Hole; MHRD: Macular Hole Retinal Detachment; MTM: Myopic Traction Maculopathy; OCT angiography: Optical Coherence Tomography Angiography; PPV: Pars Plana Vitrectomy; PS: Posterior Staphyloma; RPE: Retinal Pigment Epithelium; RRD: Rhegmatogenous Retinal Detachment; SD-OCT: Spectral-Domain Optical Coherence Tomography; SRF: Subretinal Fluid; SVP: Superficial Vascular Plexus; VD: Vessel Density; VMT: Vitreomacular Traction

Correspondence to: Miguel A. Quiroz-Reyes, Institute of Ophthalmology. Conde de Valenciana Foundation, Mexico City, Mexico, Tel: +525 55 5442 1700; Fax: +525 55 1664 7180; Email: drquiroz@prodigy.net.mx

Received date: Novembre 04, 2021; **Accepted date:** November 18, 2021; **Published date:** November 25, 2021

Citation: Quiroz-Reyes MA, Quiroz-Gonzalez EA, Morales-Navarro J, Quiroz-Gonzalez MA, Moreno-Andrade B, Carranza-Casas M, et al. (2021) Structural and Perfusional Findings in Surgically Resolved Myopic Foveoretinal Detachment Eyes and those in Early Stages of Myopic Traction Maculopathy. J Clin Exp Ophthalmol. 12:893

Key messages

• Myopic foveoschisis and foveoretinal detachment, as part of the early stages of Myopic Traction Maculopathy (MTM) are progressive degenerative conditions.

• These early stages of MTM are generally asymptomatic and detected circumstantially.

• The early stages of these conditions showed substantial perfusional alterations in retinal microcirculation and quantitative evaluation of vessel density.

• The optical coherence tomography angiography assessment demonstrated significant macular perfusion alterations and quantitative vessel density abnormalities among non-operated eyes with myopic foveoschisis and fully surgically resolved foveomacular detachment.

BACKGROUND

Myopia is an increasingly prevalent condition that represents a global public health problem. An estimated USD 244 billion in potential productivity was lost globally in 2015 because of visual impairment caused by uncorrected myopia. The prevalence of myopia is expected to reach 50% of the global population by 2050 [1].

Myopia is defined by the World Health Organization (WHO) as a refractive error with a spherical equivalent of less than or equal to -0.5 diopters [1]. High myopia is defined by a greater myopic refractive error, however, it is distinct from Pathologic Myopia (PM) that is characterized by myopic lesions in the posterior segment of the eye. PM is estimated to affect up to 3% of the global population, and the myopic lesions in the fundus can include the presence of a Posterior Staphyloma (PS) and myopic maculopathy more severe than diffuse chorioretinal atrophy [2].

Among the patients with PM, 30% can develop Myopic Traction Maculopathy (MTM) in the presence or absence of PS. MTM has a varied clinical presentation that can include inner, outer, partial or full-thickness macular holes, macular detachment, and maculoschisis [3,4]. MTM gradually worsens with time, and very rarely does it spontaneously resolve; therefore, early treatment is crucial [5].

Given the complexity of MTM, with its different clinical manifestations, few classification proposals have been put forward. The most recent classification proposed was by Parolini et al. and termed the MTM Staging System [3,4]. The system describes four MTM retinal stages (1-4) and three foveal stages (a-c) in the evolution of MTM. Stages 1 and 2 represent the earliest stages of MTM, while the final stages 3 and 4 were associated with retinal detachment. The increase in stages was shown to correlate to a decrease in Best-Corrected Visual Acuity (BVCA) over time [4].

There has been limited consensus on treating MTM with the main treatments being applied, including Pars Plana Vitrectomy (PPV), macular buckle technique, classical or modified ILM peeling, and autologous ILM or full-thickness neuroretinal transplantation. The treatments attempt to address the four sources of traction on the retinal surface: the Internal Limiting Membrane (ILM), Epiretinal Membrane (ERM) proliferation, adherent vitreous cortex, and vitreomacular traction. PPV is the most common treatment for MTM, all treatments used have produced varying levels of success [5,6].

Myopic Macular Degeneration (MMD) is a sight-threatening condition that occurs in individuals with high myopia, which is defined as a refractive error with a spherical equivalent >-6.0 diopters or an axial length>26.5 mm, MMD is at times accompanied by diffuse or patchy macular atrophy with or without lacquer cracks and may also lead to macular Bruch's membrane defects, chorioneovascular proliferation, and Myopic Traction Maculopathy (MTM) [6].

Highly myopic eyes with macular Myopic Foveoschisis (MF) and myopic Foveoretinal Detachment (FRD) naturally progress to macular hole formation [7,8]. MF was first identified by Takano and Kishi in 1999 based on Optical Coherence Tomography (OCT) cross-sectional views and was found to affect 34% of highly myopic eyes with PS [9-11]. Myopic foveoschisis and FRD are considered the early stages of MTM worldwide. These conditions remain stable long term and may slowly progress to severe forms of FRD or macular holes with or without Macular Hole Retinal Detachment (MHRD).

Recently, the perfusional, qualitative, and quantitative evaluation of Vessel Density (VD) at the macular level has recently changed the evaluation spectrum and management of different macular pathologies [12,13]. However, published data on long-term macular perfusional findings and quantitative VD evaluation of non-operated MF and FRD *vs.* surgically resolved myopic FRD are limited. Therefore, we selected surgical cases that met the criteria designed to minimize possible confounding variables. The present study aimed to compare the quantitative data on macular microcirculation in the control emmetropia, control high myopia, non-surgical observational group (non-operated eyes with MF/FRD), and operated eyes in which FRD resolved completely after macular surgery.

MATERIALS AND METHODS

Study design and patient selection

The data for the study were collected retrospectively from the Retina Department at the Institute of Ophthalmology Hospital, Retina Specialists at the American British Cowdray Hospital; and Juarez Hospital in Mexico City between October 2017 and April 2021. The institutional review board of each facility approved the study and provided access to the patients' medical records for analysis (no approval or reference number is provided for retrospective studies by institutions in Mexico City). Written informed consent was obtained from all patients in accordance with the institutional guidelines. Data are available from the Imagenology and Psychophysics Laboratory at the retina departments of the three institutions. The study groups and inclusion criteria are listed in Table 1.

Table 1: Study groups and inclusion criteria.

Study group	Inclusion criteria
Control emmetropia (n=25)	No previous disease history, BCVA ≥ 20/20, intraocular pressure ≥ 10 to ≤ 21 mmHg, no abnormalities on dilated fundus examination and OCT scan
Control high myopia (n=20)	Spherical equivalent refractive error of >-6.0° diopters or axial length>26.5 mm
Non-surgical observational (n=28)	Non-operated eyes, diagnosis of myopic foveoschisis or myopic foveoretinal detachment
Surgically treated (n=45)	Consecutively enrolled patients who underwent vitrectomy with successful and uncomplicated macular surgery using the fovea-sparing ILM surgical technique for symptomatic myopic FRD (32 eyes; 29 consecutive patients) and 13 eyes with myopic FRD treated with uncomplicated classical ILM removal surgery

Note: BCVA: Best-Corrected Visual Acuity; FMD: Foveomacular Detachment; ILM: Internal Limiting Membrane; OCT: Optical Coherence Tomography

None of the eyes included in the study received intravitreal injections or laser photocoagulation during the study period. Study participants were matched for age, sex, study period, and follow-up duration. In all institutions, patients were evaluated following the standardized protocol of every month for six months and then every six months until the last follow-up visit. The same surgeon performed the surgeries across the three referral institutions, which used the same inclusion and exclusion criteria.

In the surgical study group, which comprised symptomatic highly myopic patients with evidence of a progressive decrease in BCVA, a three-port pars plana vitrectomy was performed. All of the selected eyes had an axial length>26.5 mm with no evidence of patchy foveal-affected chorioretinal atrophy, diffuse macular chorioretinal atrophy, or quiescent or active myopic choroidal neovascularization according to the ATN classification [14]. In the non-surgical and surgical groups, a diagnosis of MF or myopic FRD traction maculopathy was confirmed using Spectral-Domain OCT (SD-OCT) findings consistent with internal or external schisis-like foveomacular thickening, presence or absence of epiretinal membrane and residue of hyaloidal cortical remnants, central submacular presence of subretinal fluid, and no evidence of partial or full-thickness macular holes on SD-OCT examination. Only patients who completed a follow-up period of at least six months were statistically analyzed.

Examinations

General ophthalmic evaluation and preoperative assessments were conducted in all patients, including a BCVA assessment, regular Amsler grid test, slit-lamp biomicroscopic examination, and detailed fundus evaluation using a panfundoscopic contact lens and indirect ophthalmoscopy. Cross-sectional images of the macular region were acquired along the horizontal plane through the foveal center using SD-OCT (RTVue-XR platform SD-OCT; Optovue, Inc., Fremont, CA, USA), and the axial lengths were measured using partial coherence laser interferometry (Zeiss IOL Master 700; Carl Zeiss Meditec AG, Oberkochen, Germany). The presence of PS in both groups was confirmed using B-scan ultrasonography (ultrasound A and B, Quantel Medical, Du Bois Loli, Auvergne, France) and indirect ophthalmoscopy.

Preoperative and postoperative microstructural evaluations were performed using SD-OCT and a swept-source DRI OCT Triton device (Topcon Medical Systems, Inc., Oakland, CA, USA). Cross-sectional images of the macular region were acquired along the horizontal plane through the foveal center. The BCVA in the Snellen unit was converted to the logarithm of the minimum angle of resolution (logMAR) units. Pre- and postoperative perfusional and quantitative VD evaluations were performed using an OCT angiography device (RTVue XR OCT Avanti with AngioVue Software; OptoVue, Inc., Fremont, CA, USA) and a commercially available Avanti SD-OCT device (OptoVue, Inc.). The AngioVue OCT angiography system was used for imaging. This system uses a split-spectrum amplitude-decorrelation angiography software algorithm and acquires 70,000 A-scans/s to compose OCT angiography volumes consisting of 304 × 304 A-scans, achieving high axial resolution at depths of up to 5 μm and minimizing motion artifacts. Each OCT angiography cube scan consisted of 304 × 304 A-scans within a 3 × 3 mm square centered on the fovea, which yielded 304 B-scans. Each B-scan output displayed an average of at least two individual scans. The AngioVue software includes a built-in projection artifact removal algorithm and has four default En face retinal imaging settings for automatic segmentation of the Superficial Vascular Plexus (SVP), Deep Vascular Plexus (DVP), outer retina layer, and choriocapillaris plexus. Auto-segmentation errors were corrected by automated adjustment of the contour and location of each segmentation line. An independent reader interpreted the imaging data from each institution. The quality of the OCT angiography images was assessed using the signal strength index.

The Foveal Avascular Zone (FAZ) area in the SVP was evaluated by analyzing En face images saved as PNG files in the AngioVue system. Each FAZ area was automatically outlined following AngioAnalytics with angiometrics in the AngioVue software system to facilitate the measurements. Only scans with a signal strength index of>46 were included. Projection artifacts were automatically excluded with digital outlining of the FAZ in the SVP. The superficial FAZ area was quantitatively calculated. A built-in tool in the AngioVue system was used to measure the VD [15,16]; a quantitative evaluation of the SVP and DVP was then automatically generated. We defined VD as the proportion of vessel area with blood flow over the total measured area. We defined whole-macula VD and choriocapillaris subfoveal flow area as density values within a 3 × 3 mm square and a 1-mm-diameter circle automatically selected in the foveal area, respectively.

Surgical procedures

A single surgeon (MAQR) performed a standard 25-G three-port pars plana vitrectomy under local anesthesia and sedation in the surgical group. In addition to the core vitrectomy, triamcinolone acetonide–assisted (Kenalog 40 mg/mL; Bristol-Myers, New York, NY, USA) removal of the cortical vitreous from the surface of the retina was performed using a silicone-tipped cannula and active suction with a focus on achieving a free and mobile posterior hyaloid membrane and leaving the superficial foveal tissue (foveal roof) untouched. The technique was standardized, and surgical macular evaluation and revision were performed in all cases using trypan blue 0.15% ophthalmic solution (Membrane Blue; Dutch Ophthalmic USA) as an adjuvant dye to stain cortical vitreous remnants or ERMs. As a second-step macular surgery, 0.15 mL of a 0.25 mg/mL (0.025%) diluted isomolar solution (pH 7.4) of Brilliant Blue G (BBG) dye was used to selectively stain the ILM and manipulate it cautiously to accomplish adequate fovea-sparing surgical ILM removal without peeling the dyed foveocentral ILM. In most cases, the ILM was peeled off, leaving the fovea untouched with its corresponding foveocentral ILM as mentioned above. Only eyes in which this technique was completed and uncomplicated were included in this study. This procedure was performed using a 25-G vitrectomy cut and suction instrument (Alcon Constellation Vision System; Alcon Labs, Fort Worth, TX, USA) and 25-G 0.44 ILM forceps (Grieshaber Revolution DSP ILM forceps; Alcon Labs) along with a 25-G Finnesse ILM flex loop microinstrument (Grieshaber; Alcon Labs) to facilitate ILM flap manipulation. A non-expandable bubble with a 15% perfluoropropane gas mixture was used as a long-acting tamponade. The classic ILM peeling technique consisted of staining and removal of the ILM from the macular vascular arcade to the vascular arcade, ensuring there were no remnants of the ILM left on the foveal surface. In 12 phakic eyes, phacoemulsification and intraocular lens implantation were performed, and the lens status was not considered a variable in the postoperative analysis. Only eyes with structurally fully resolved myopic FRD in which these techniques were completed and uncomplicated were included in this study.

Study outcomes

The primary outcome measure included the comparative OCT angiographic findings in three untreated groups (control emmetropia, control high myopia, and non-surgical observational group) to the postoperative OCT angiographic findings of the surgically treated group and structurally fully resolved myopic FRD. The secondary outcome measures included long-term final postoperative BCVA and its correlation with SD-OCT and OCT angiography data.

Statistical analysis

Data were collected in Microsoft Excel and transferred to GraphPad Prism version 8.2.1. The data were assessed for normal distribution using the Shapiro-Wilk test. Statistical tests were chosen based on data normality: one-way analysis of variance was used for parametric analyses, while the Kruskal-Wallis test was used for non-parametric analyses. Dunnett's test was used for the post-hoc analyses. The Wilcoxon matched signed-rank test was used to compare preoperative and postoperative BCVA. Statistical significance was set at $p<0.05$. Multivariate regression analysis was used to identify possible correlations between logMAR, Ellipsoid Zone (EZ) defects, and external limiting membrane defects with various OCT and non-OCT biomarkers. In the surgical group, multivariate regression analysis was used to identify possible correlations between changes in logMAR pre and post-surgery with relevant biomarkers.

RESULTS

A total of 118 eyes (104 participants) were included in the study: 25 in the control emmetropic group, 20 in the healthy control myopic group, 28 in the non-surgical observational group and 45 in the surgical group. The follow-up duration was 6-43 months with a mean of 23.86 ± 12.10 months (mean ± SD). Baseline clinical characteristics of the patients are shown in Table 2. The structural and perfusional characterisitics shown in multipanel (Figures 1-3).

The baseline BCVA was similar between the two control groups (control emmetropic and control high myopia) and the non-surgical observational group ($p>0.05$), whereas it differed from that of the surgical group ($p<0.0001$). The postoperative BCVA in the surgical group (median BCVA, 0.30 logMAR [min to max, 0.09-1.00]) remained poorer than that all other groups ($p<0.0001$). The improvement in visual acuity in the surgically treated group was highly significant ($p<0.0001$) after surgery (Figures 1-3).

Structural results

In the surgical group, the mean preoperative evolution time for FRD was 6.20 ± 3.60 months, while the mean postoperative time for its resolution was 4.60 ± 1.98 weeks. The postoperative BCVA was measured and compared between 20 eyes (57.1%) with normal OCT results and 15 (42.9%) with abnormal OCT results to determine whether surgery outcomes correlated with the macular alterations observed on OCT. The postoperative median BCVA in the surgical group was 0.30 logMAR (min to max, 0.09-1.00). A one-sided permutation test found only tentative statistical evidence ($p=0.078$) for the difference in BCVA between those with abnormal OCT findings versus those with normal OCT findings. The postoperative structural findings are summarized in Table 3. The superficial FAZ area was significantly greater in the high myopia, non-surgical observational, and surgical groups ($p<0.05$). Superficial foveal VD was significantly lower in the untreated observational group. Central Subfield Foveal Thickness (CSFT) was significantly higher in the observational group and significantly lower in the surgery group (both $p<0.05$). The superficial FAZ area was significantly correlated with superficial perifoveal VD ($p=0.031$), and superficial foveal VD (%) was significantly correlated with deep foveal VD, deep parafoveal VD, deep perifoveal VD, and superficial and deep whole macular VD (all $p<0.05$).

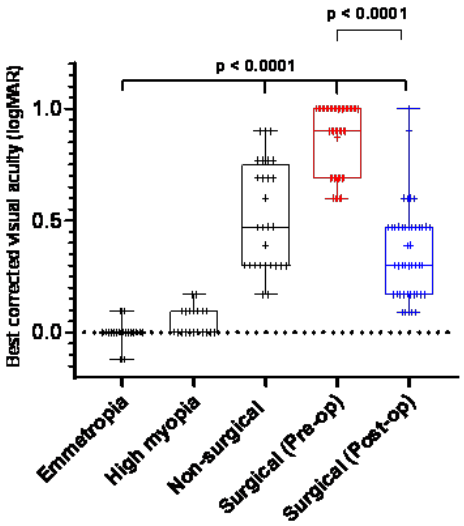

Figure 1: BCVA in the control emmetropic group differed from those of non-surgical observational and surgical pre-/postoperative groups ($p<0.05$). The graphs show the median with range.

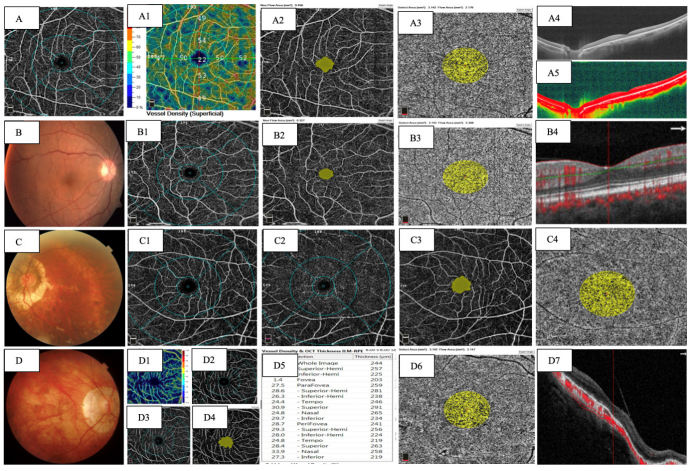

Figure 2: Normal emmetropic and healthy myopic control eyes: A: normal Superficial Vascular Plexus (SVP) obtained using inbuilt software (mm^2). A1: The color overlays on the OCTA angiography image indicate a normal vessel density perfusion index in the key to the left. A2: Foveal Avascular Zone (FAZ) area of 0.456 mm^2. A3: Choriocapillaris flow perfusion index of 2.176 mm^2 in a selected area of 3.142 mm^2. A4: Enhanced High Definition (HD) 12 mm line horizontal B scan designed to show more detail in the retina and choroid. A5. Enhanced HD line horizontal 12 mm horizontal B scan designed to show more detail in the vitreoretinal interface with brighter colors. B: Fundus color photo in a normal emmetropic eye. B1: Normal SVP with above the normal Vessel Density (VD) perfusion index. B2: Normal FAZ area of 0.327mm^2. B3: Normal choriocapillaris flow area with a perfusion index of 2.308 mm^2. B4: Normal SD-OCT horizontal B scan, automatic green segmentation, and measurements line differentiating inner from the deeper retina. Red dots indicate intraretinal and choriocapillaris vascular flow. External biomarkers, such as the Ellipsoid Zone (EZ) and External Limiting Membrane (ELM) line, are well delineated. C: Color fundus of a 20/20 highly myopic eye. C1: Corresponding SVP with normal perfusion indices (VD and flow index) in a healthy highly myopic eye. C2: Corresponding deep vascular plexus between normal range. C3: Foveal avascular zone with normal FAZ area. C4: Normal choriocapillaris flow area with a normal perfusion index in the control healthy myopic eye. D: Normal healthy highly myopic eye with 29.3 mm in axial length and 20/20 best-corrected visual acuity. D1: The color overlays on the OCTA angiography image indicate a normal VD perfusion index in the key to the right. D2: Normal VD perfusion index in the SVP. D3: Quantitative normal VD perfusion index in the DVP. D4: Large but symmetrical normal FAZ with an average area in mm^2. D5: Corresponding VD perfusion index and retinal thickness table values at different macular subfields. D6: Normal choroidal flow area of 2.147 mm^2, there is normality in perfusion indices (VD and flow index). D7: Corresponding horizontal SD-OCT B scan with a normal profile, distinct outer biomarkers, hyaloidal line attached to the macula, and good choroidal flow represented by red dots beneath retinal pigment epithelium.

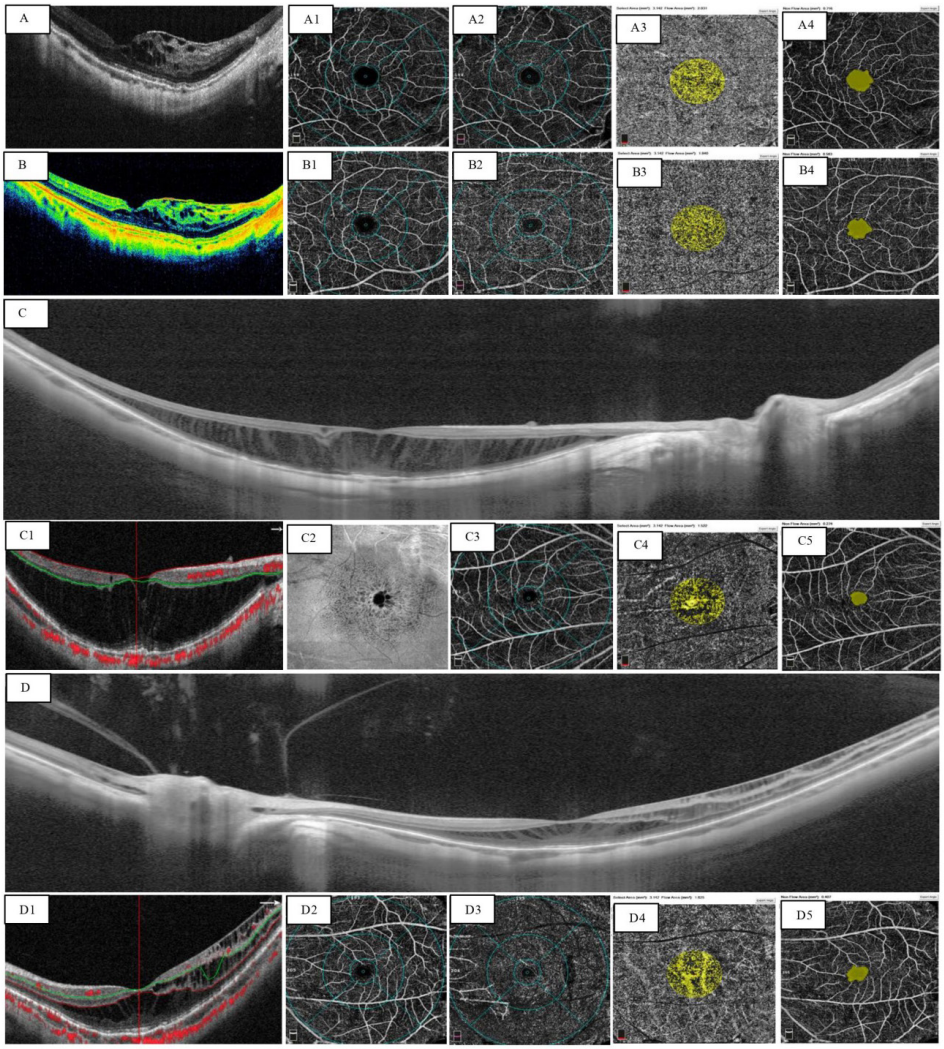

Figure 3: Non-surgical study eye (Observational): A: Myopic Foveoschisis (MF) with Epiretinal Membrane (ERM) proliferation, internal and external foveoschisis, and schisis-like macular thickening. A1: Corresponding superficial vascular plexus (SVP) with normal macular perfusion indices (vessel density and flow index). A2: Deep Vascular Plexus (DVP) showing a smaller deep foveal avascular zone. A3: Corresponding choriocapillaris flow area of 2.031 mm^2 considered as a normal range perfusion index (VD and flow index). A4. Corresponding FAZ area of 0.716 mm^2 higher than mean in the same patient. B: Colour structural MF with a focal myopic FRD, ERM, and remarkable schisis-like macular thickening. B1: SVP with a normal quantified VD perfusion index. B2: DVP with a smaller than mean FAZ. B3: Normal choriocapillaris vascular flow area of 1.840 mm2 with normal macular perfusion indices (VD and flow index). B4. Corresponding non-flow FAZ area of 0.543 considered above average. C: Enhanced High-Definition (HD)12 mm line horizontal B scan of retinal MF with Ellipsoid Zone (EZ) and External Limiting Membrane (ELM) line disruptions, severe schisis in the Outer Plexiform Layer (OPL). C1: SD-OCT corresponding horizontal B scan with a segmentation green line and red dots corresponding to retinal and choroidal vessels, schisis-like macular thickening, and severe schisis of the OPL are depicted. C2: Corresponding petaloid-like appearance on the En face image. C3: Automated VD quantification in the SVP considered with a perfusion index lower than average. C4: Quantification of choriocapillaris flow area is 1.522, within the normal mean. C5: FAZ area is smaller than mean. D: Enhanced high-definition 12 mm line horizontal B scan of retinal MF with EZ and ELM line disruptions, severe schisis in the OPL, the posterior hyaloid is still attached to the peripapillary and macular region, there is schisis in the inner nuclear layer and in the nerve fiber layer temporal to the fovea with overlying stretched Internal Limiting Membrane (ILM), severe schisis of the OPL on the temporal side. D1: Corresponding horizontal SD-OCT B scan with segmentation green and red lines and red dots corresponding to retinal and choroidal vessels, the schisis-like macular thickening and severe schisis of the OPL are shown; stretched ILM is depicted over the temporal aspect of the fovea. D2: Perfusion indices (VD and flow index) in the SVP were quantified as lower than normal. D3: DVP depicts superficial vessel shadowing artifacts (ghost vessels) and extrafoveal lacquers with lower-than-normal perfusion indices (VD and flow index). D4: Choriocapillaris flow area of 0.825 was considered within normal range. D5: FAZ non-flow area of 0.407, within normal range.

Table 2: Baseline clinical data by study group.

Study group	Female sex (%)	Median age (min to max, years)	Preoperative median BCVA (min to max, logMAR)	Axial length (mean ± SD, mm)
Control emmetropic group (n=25)	76	52 (22 to 66)	0 (-0.12 to 0.09)	20.53 ± 0.09
Control myopic group (n=20)	70	60 (48-70)*	0 (0.00-0.09)	29.45 ± 1.49*
Non-surgical observational group (n=28)	75	59 (48-70)*	0.47 (0.17-0.90)*	29.49 ± 1.53*
Surgical group (n=45)	77.7	59 (43-76)*	0.9 (0.60-1.00)*	29.35 ± 1.51*
P value	0.28	0.002	0.0001	0.0001

Note: *Indicates the groups where data differed significantly (p<0.05) from the control emmetropic eyes. BCVA: Best-Corrected Visual Acuity; SD: Standard Deviation

Table 3: Quantitative evaluation of macular perfusion by study group.

	Superficial FAZ area (mm^2, mean ± SD)	Superficial foveal VD (%, mean ± SD)	Deep foveal VD (%, mean ± SD)	Superficial parafoveal VD (%, mean ± SD)	Deep parafoveal VD (%, mean ± SD)	Superficial perifoveal VD (%, mean ± SD)	Deep perifovea VD (%, mean ± SD)	Superficial whole macula VD (%, mean ± SD)	Deep whole macula VD (%, mean ± SD)	Choriocapillaris flow area (mm^2, mean ± SD)	CSFT (µm, mean ± SD)
Control emmetropic (n=25)	0.33 ± 0.04	27.17 ± 3.40	31.39 ± 3.06	58.76 ± 3.03	59.17 ± 2.60	54.86 ± 3.29	56.08 ± 3.13	56.93 ± 4.27	58.50 ± 3.66	2.51 ± 0.24	246.40 ± 21.12
Control high myopia (n=20)	0.647 ± 0.12*	27.57 ± 3.91	32.11 ± 4.27	55.24 ± 2.56	54.98 ±2.051*	45.62 ± 4.68*	47.88 ± 4.17*	46.35 ± 3.36*	48.55 ± 2.65*	2.25 ± 0.22*	264.9 ± 37.91
Non-surgical (n=22)	0.60 ± 0.05*	21.74 ± 3.99*	26.08 ± 3.33*	43.21 ± 9.56*	45.58 ± 2.96*	42.67 ±3.24*	44.04 ± 2.65*	43.7 ± 1.63*	45.15 ± 1.31*	1.97 ± 0.23*	586 ± 86.01*
Surgically corrected (n=33)	0.74 ± 0.32*	24.83 ± 4.094	28.15 ± 4.24*	49.36 ± 6.35*	51.26 ± 6.25*	49.20 ± 5.58*	49.99 ± 5.50*	48.13 ± 4.42*	47.75 ± 9.65*	1.78 ± 0.29*	190.30 ± 23.36*
Comparison with control emmetropic (p value)	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001

Note: *Indicates the groups where data differed significantly (p<0.05) from the control emmetropic group. CSFT: Central Subfield Foveal Thickness; FAZ: Foveal Avascular Zone; SD: Standard Deviation; VD: Vessel Density

Perfusional and structural findings and comparison between groups

Table 4 summarizes the postsurgical structural findings in the surgical group and the structural findings in the emmetropic, healthy myopic, and non-surgical groups. Analysis of variance with Tukey's post-hoc correction was used to test for differences between all pairwise study groups. The test results, including intergroup adjusted p values and differences, are summarized in Table 5.

The data generally show a larger superficial FAZ area, lower VD, and smaller choriocapillaris flow area in the myopic versus control emmetropic group. The superficial FAZ area did not differ between the myopic groups, including the non-surgical and surgical groups. All VD parameters were statistically significant, the non-surgical group consistently had lower VD values than the healthy myopic group. Similarly, the surgical group consistently showed significantly higher VD values than the non-surgical group except for deep foveal VD (p=0.202) and deep whole macular VD (p=0.404).

The choriocapillaris flow area was largest in the emmetropic group, followed by the healthy myopic, non-surgical, and surgical groups, and the differences being statistically significant. CSFT was significantly higher in the non-surgical myopic group (p<0.001) than in the healthy myopic and emmetropic groups, but it returned to close to the emmetropic level in the surgical group. EZ and External Limiting Membrane (ELM) defects were both higher in the non-surgical and surgical groups, with the greatest incidence in the surgical groups.

Table 4: Perfusional value (index) and structural characterization by group.

	Emmetropic	Healthy myopic	Non-surgical	Surgical
		Reported as mean (SD)		
Superficial FAZ area, mm^2	0.34 (0.04)	0.65 (0.12)	0.6 (0.05)	0.75 (0.33)
Superficial foveal VD, %	27.17 (3.41)	27.57 (3.91)	21.74 (3.99)	24.83 (4.09)
Deep foveal VD, %	31.39 (3.06)	32.11 (4.27)	26.08 (3.33)	28.15 (4.24)
Superficial parafoveal VD, %	58.76 (3.03)	55.24 (2.57)	43.21 (9.56)	49.36 (6.35)
Deep parafoveal VD, %	59.17 (2.61)	54.98 (2.05)	45.58 (2.97)	51.26 (6.25)
Superficial perifoveal VD, %	54.86 (3.3)	45.62 (4.68)	42.67 (3.25)	49.2 (5.58)
Deep perifoveal VD, %	56.08 (3.14)	47.88 (4.17)	44.04 (2.65)	49.99 (5.5)
Superficial whole macula VD, %	56.93 (4.28)	46.35 (3.37)	43.7 (1.63)	48.13 (4.42)
Deep whole macula VD, %	58.5 (3.67)	48.55 (2.65)	45.15 (1.31)	47.75 (9.65)
Choriocapillaris flow area, mm^2	2.51 (0.24)	2.25 (0.23)	1.99 (0.24)	1.78 (0.29)
CSFT, micron	246.4 (21.12)	264.85 (37.91)	586 (86.01)	190.27 (23.36)
		Reported as incidence (%)		
EZ defect	0 (0%)	1 (5%)	4 (14.3%)	11 (24.4%)
ELM defect	0 (0%)	2 (10%)	5 (17.9%)	14 (31.1%)

Note: CSFT: Central Subfield Foveal Thickness; ELM: External Limiting Membrane; EZ: Ellipsoid Zone; SD: Standard Deviation; VD: Vessel Density

Table 5: Analysis of variance test results by group.

	Healthy myopic–emmetropic	Non-surgical–emmetropic	Surgical–emmetropic	Non-surgical–healthy myopic	Surgical– healthy myopic	Surgical– non-surgical
			Reported in adjusted p value[a] (difference in group means)			
Superficial FAZ area	<0.001	<0.001	<0.001	0.892	0.309	0.053
	-0.31	-0.26	-0.41	(-0.04)	-0.1	-0.14
Superficial foveal VD	0.986	<0.001	0.109	<0.001	0.066	0.024
	-0.4	(-5.44)	(-2.34)	(-5.83)	(-2.74)	-3.09
Deep foveal VD	0.921	<0.001	0.009	<0.001	0.002	0.202
	-0.72	(-5.31)	(-3.24)	(-6.03)	(-3.96)	-2.07
Superficial parafoveal VD	0.224	<0.001	<0.001	<0.001	0.005	0.002
	(-3.52)	(-15.54)	(-9.4)	(-12.03)	(-5.88)	-6.15
Deep parafoveal VD	0.006	<0.001	<0.001	<0.001	0.012	<0.001
	(-4.19)	(-13.59)	(-7.9)	(-9.4)	(-3.72)	-5.69
Superficial perifoveal VD	<0.001	<0.001	<0.001	0.146	0.027	<0.001
	(-9.24)	(-12.18)	(-5.65)	(-2.95)	-3.58	-6.53
Deep perifoveal VD	<0.001	<0.001	<0.001	0.02	0.289	<0.001
	(-8.2)	(-12.04)	(-6.09)	(-3.84)	-2.11	-5.95
Superficial whole macula VD	<0.001	<0.001	<0.001	0.107	0.334	<0.001
	(-10.59)	(-13.23)	(-8.8)	(-2.65)	-1.79	-4.43
Deep whole macula VD	<0.001	<0.001	<0.001	0.274	0.966	0.404
	(-9.95)	(-13.35)	(-10.75)	(-3.4)	(-0.8)	-2.6
Choriocapillaris flow area	0.005	<0.001	<0.001	0.007	<0.001	0.022
	(-0.26)	(-0.52)	(-0.73)	(-0.26)	(-0.47)	(-0.2)
CSFT	0.557	<0.001	<0.001	<0.001	<0.001	<0.001
	-18.45	-339.6	(-56.13)	-321.15	(-74.58)	(-395.73)

	Reported in adjusted p value (difference in incidence)					
EZ defect	0.963	0.283	0.003	0.61	0.025	0.391
	-1	-4	-11	-3	-10	-7
ELM defect	0.814	0.175	<0.001	0.697	0.017	0.238
	-2	-5	-14	-3	-12	-9

Note: [a]Adjusted p<0.05 values are highlighted in gray. CSFT: Central Subfield Foveal Thickness; ELM: External Limiting Membrane; EZ: Ellipsoid Zone; FAZ: Foveal Avascular Zone; VD: Vessel Density

Correlation between BCVA, EZ defect, ELM defect, and biomarkers

Multivariate regression analysis revealed biomarkers for functional BCVA (Tables 6 and 7) and structural defects in the EZ (Table 8) and ELM (Table 9) layers. The analysis results showed that BCVA was positively correlated with choriocapillaris flow area and negatively correlated with CSFT (analysis done with BCVA converted to logMAR scale, which was negatively correlated with choriocapillaris flow area and positively correlated with CSFT). In the surgical group, the change in BCVA before versus after surgery was analyzed using 14 biomarkers, but none was statistically significant. Structural defects in the EZ were positively correlated with the superficial FAZ area and ELM defects. Similarly, structural defects in ELM were positively correlated with EZ defects and negatively correlated with deep whole macular VD.

Three representative cases

Clinical case 1: A 49-year-old symptomatic woman complained of a seven-month history of metamorphopsia and progressive visual loss in her right eye. The preoperative BCVA visual acuity of the right eye was 20/160 (0.90 logMAR), with a refractive error of -21.00/+3.00 × 70 and intraocular pressure of 10 mmHg. The right eye had an axial length of 29.76 mm with PS, and the fundus photograph revealed myopic FRD. The preoperative SD-OCT findings were consistent with ERM proliferation, schisis-like macular thickening, and a remarkable amount of central macular Subretinal Fluid (SRF). Macular surgery was performed using the modified fovea-sparing ILM peeling technique. The eye underwent a second procedure using macular surgical revision with adjuvant BBG dye to identify any ILM remnants and fluid-air exchange with a non-expandable 15% perfluoropropane gas mixture due to the refractory FRD and increasing foveal symptomatology. At the 35-month follow-up visit, the foveomacular region remained attached, and the patient retained a final BCVA of 20/40 (0.30 logMAR). There was evidence of extrafoveal, nasal, residual, and very shallow SRF. In addition, some recognizable SD-OCT biomarkers, such as an irregular foveal contour and internal and external neuroretina lines without total restoration of the central subfoveal ellipsoid band and the ELM line, were noted. A color fundus image showed the presence of myopic changes over the posterior pole with well-delineated areas of extrafoveally located peripapillary chorioretinal atrophy. An autofluorescence image depicted only very mild RPE foveal changes (Figure 4).

Table 6: Correlation analysis with best-corrected visual acuity.

	Coefficient estimate	Standard error	P-value[a]
Superficial FAZ area	0.05645	0.10318	0.5857
Superficial foveal VD	-0.00468	0.00723	0.5191
Deep foveal VD	0.00204	0.00715	0.7766
Superficial parafoveal VD	-0.00086	0.0047	0.85487
Deep parafoveal VD	-0.00876	0.00959	0.36352
Superficial perifoveal VD	0.02995	0.01861	0.11125
Deep perifoveal VD	-0.01497	0.02179	0.49413
Superficial whole macula VD	0.00921	0.0184	0.61809
Deep whole macula VD	-0.02171	0.01967	0.27281
Choriocapillaris flow area	-0.18412	0.06775	0.00795
CSFT	0.00073	0.00018	0.00008
EZ defect	0.02681	0.06668	0.68857
ELM defect	-0.06262	0.07116	0.38128

Note: [a]Adjusted p<0.05 values are highlighted in gray. CSFT: Central Subfield Foveal Thickness; ELM: External Limiting Membrane; EZ: Ellipsoid Zone; FAZ: Foveal Avascular Zone; VD: Vessel Density

Table 7: Correlation analysis with changes in best-corrected visual acuity.

	Coefficient estimate	Standard error	P-value[a]
Superficial FAZ area	-0.07371	0.19146	0.70474
Superficial foveal VD	0.00355	0.02002	0.86133
Deep foveal VD	0.00449	0.02169	0.83826
Superficial parafoveal VD	-0.00182	0.03389	0.95784
Deep parafoveal VD	0.04379	0.05228	0.41324
Superficial perifoveal VD	-0.02044	0.08838	0.8197
Deep perifoveal VD	0.01467	0.11476	0.8997
Superficial whole macula VD	-0.01587	0.06577	0.81204
Deep whole macula VD	-0.02425	0.04694	0.61173
Choriocapillaris flow area	0.10506	0.19208	0.5911
CSFT	-0.00038	0.00251	0.88173
EZ defect	0.03026	0.13642	0.82697
ELM defect	-0.04245	0.18626	0.82227
Macula surgery complication	0.0945	0.13916	0.50576

Note: [a]Adjusted p<0.05 values are highlighted in gray. BCVA: Best-Corrected Visual Acuity; CSFT: Central Subfield Foveal Thickness; ELM: External Limiting Membrane; EZ: Ellipsoid Zone; FAZ: Foveal Avascular Zone; VD: Vessel Density

Table 8: Correlation analysis of ellipsoid zone defect.

	Coefficient estimate	Standard error	P-value[a]
Superficial FAZ area	3.83552	1.86337	0.03955
Superficial foveal VD	-0.09276	0.13738	0.49952
Deep foveal VD	0.03275	0.14763	0.82445
Superficial parafoveal VD	-0.03464	0.08335	0.67769
Deep parafoveal VD	0.23484	0.22765	0.30226
Superficial perifoveal VD	-0.1999	0.3485	0.56623
Deep perifoveal VD	0.46077	0.56953	0.4185
Superficial whole macula VD	-0.33562	0.50016	0.5022
Deep whole macula VD	-0.17295	0.3665	0.63701
Choriocapillaris flow area	-2.7476	1.60754	0.08741
CSFT	0.0016	0.003	0.59416
ELM defect	3.24898	1.1083	0.00337

Note: [a]Adjusted p<0.05 values are highlighted in gray. CSFT: Central Subfield Foveal Thickness; ELM: External Limiting Membrane; FAZ: Foveal Avascular Zone; VD: Vessel Density

Table 9: Correlation analysis with external limiting membrane defect.

	Coefficient estimate	Standard error	P-value[a]
Superficial FAZ area	-4.72638	3.60924	0.19036
Superficial foveal VD	0.30519	0.17883	0.08789
Deep foveal VD	0.16332	0.16091	0.31014
Superficial parafoveal VD	0.19074	0.24865	0.44303
Deep parafoveal VD	-0.64451	0.38913	0.09767
Superficial perifoveal VD	0.62088	0.50459	0.21853
Deep perifoveal VD	-0.32737	0.66951	0.62486
Superficial whole macula VD	1.07921	0.66909	0.10675
Deep whole macula VD	-1.38178	0.61449	0.02453
Choriocapillaris flow area	-0.81409	1.57546	0.60534
CSFT	-0.00063	0.00311	0.8403
EZ defect	4.21391	1.52114	0.0056

Note: [a]Adjusted p<0.05 values are highlighted in gray. CSFT: Central Subfield Foveal Thickness; EZ: Ellipsoid Zone; FAZ: Foveal Avascular Zone; VD: Vessel Density

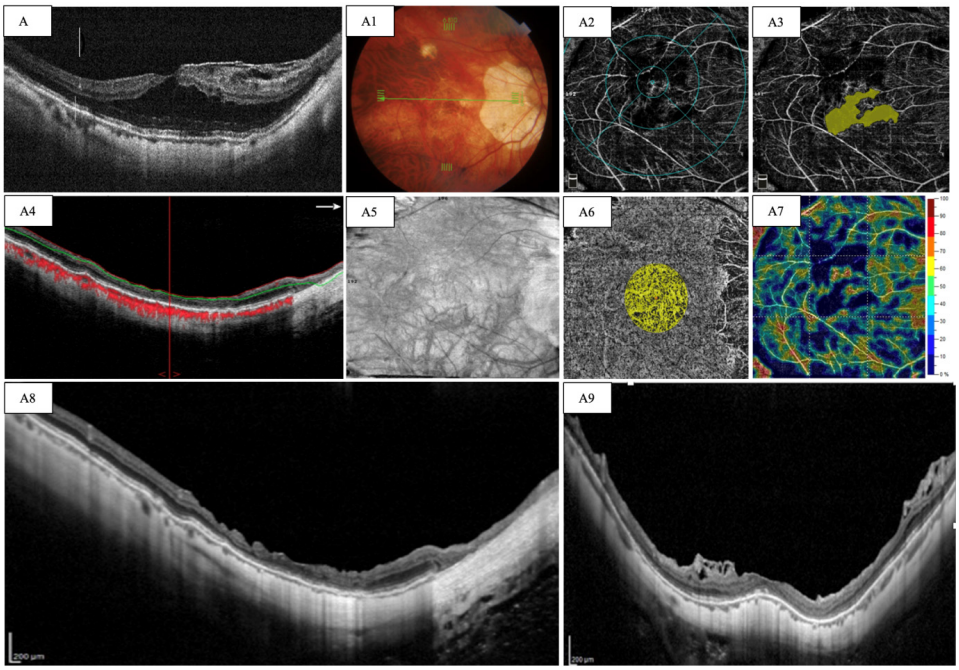

Figure 4: Surgical case 1: A: Preoperative SD-OCT image of a very complex Myopic Foveoschisis (MF)/Foveoretinal Detachment (FRD) in a very symptomatic highly myopic 43-year-old patient, with an axial length of 29.76 mm. A1: Color fundus photo of the corresponding case. A2: Superficial Vascular Plexus (SVP) showing irregular and deficient vascular flow index quantified lower than average. A3: The postoperative view of the Foveal Avascular Zone (FAZ) shows an enlarged and irregular FAZ. A4: The postoperative horizontal SD-OCT shows a complete resolution of the MF/FRD. The green and red segmentation lines depicted demonstrate diffuse retinal thinning of the inner retinal layers. There is residual schisis on the nasal side, a lack of red dots due to vessels deficiencies with a lower VD perfusion index in the superficial layers, and deep red dots consistent with choroidal circulation. A5: En face view with diffuse retinal pigment thinning. A6: Corresponding normal quantified choriocapillaris flow area perfusion index. A7: The color overlays on the OCTA angiography image indicate lower-than-normal vessel density values in the key to the right. A8, A9: Long-term postoperative cross line images showing diffuse optic nerve DONFL defects with residual subretinal fluid on the nasal side and hyaloidal remnants.

Clinical case 2: A 65-year-old symptomatic woman presented with aggravated metamorphopsia, a progressive decline in central vision, and high myopia. She had bilateral PS. The right eye had an axial length of 28.92 mm and was subjected to macular surgery due to a 12-month history of symptomatic myopic FRD. The preoperative BCVA was 20/100 (0.70 logMAR). This eye underwent three-port 25-G pars plana vitrectomy and non-foveal ILM peeling using the modified fovea-sparing technique. Fluid-air gas exchange was performed using a 15% C3F8 tamponade. At the 29-month longitudinal follow-up, the operated eye showed a postoperative BCVA of 20/25 (0.10 logMAR), no evidence of recurrent myopic FRD, and no progression to the macular hole in the swept-source SD-OCT. Fundus color photographs showed a highly myopic eye with well-defined peripapillary chorioretinal atrophy. The autofluorescence image depicted a well-delineated peripapillary RPE atrophy and highly mild pigment mottling changes over the macula consistent with dissociated optic nerve fiber layer defects (Figure 5).

Clinical case 3: A 46-year-old woman with a 3-month history of persistent, bothersome, and disabling metamorphopsia, high myopia, and moderate PS underwent 25-G three-port pars plana vitrectomy and macular surgery on the phakic right eye for symptomatic myopic foveoschisis/foveal retinal detachment on the preoperative 100 microns apart raster horizontal B scans showing a very complex MF/FRD with severe altered outer retinal layers, there is abundant amount of intraretinal middle layers fluid within schisis cavities. This eye underwent vitreous and macular surgery consisting of a modified BBG dye-assisted ILM peeling technique (fovea-sparing ILM peeling technique) and a 15% C3F8 long-acting non-expandable gas tamponade. The preoperative BCVA was 20/200 (logMAR 1.00), with PS and an axial length of 28.70 mm. At the 24-month follow-up, the final postoperative BCVA was 20/25 (logMAR 0.10) and showed a SVP with quantitative deficiencies. The OCT angiography evaluation revealed an abnormal SVP with an irregular and enlarges FAZ and choroidal vascular regional deficiencies and some compensatory choroidal flow, the deep choroidal flow and choriocapillaris flow were considered between normal range, diffuse retinal thinning and evident posterior pole deep vessels and inner scleral surface irregularities were shown on the En face evaluation (Figure 6).

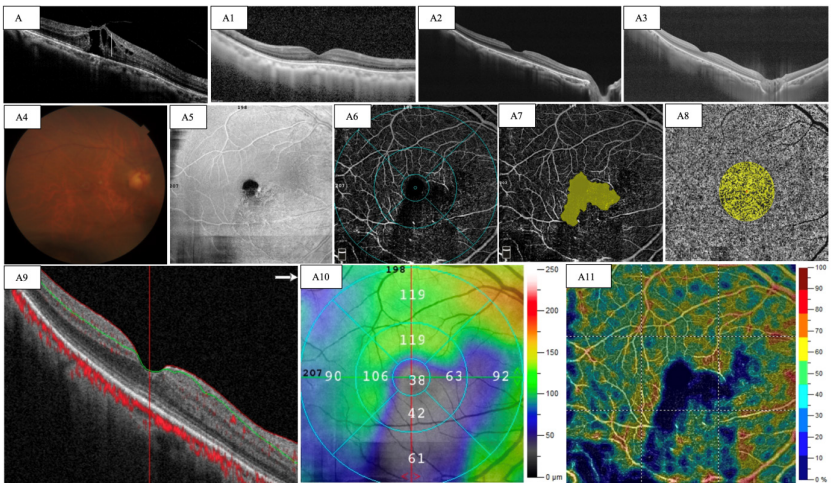

Figure 5: Surgical case 2: A: SD-OCT horizontal view of a very symptomatic highly myopic 62-year-old woman with 5 months of vision loss and severe metamorphopsia on the right eye, the axial length is 28.92 mm. There is severe focal subfoveal Foveoretinal Detachment (FRD), schisis-like retinal thickening with schisis in the inner nuclear layer on the nasal aspect of the fovea, focal vitreoretinal retinal traction is shown. The external biomarkers such as the ellipsoid zone and external limiting membrane are severely disrupted, the subfoveal choroidal vessels look normal. A1: Corresponding postoperative view of the horizontal SD-OCT where the external biomarkers look recuperated. A2: Corresponding postoperative 9 mm high-resolution horizontal scan showing a fully resolved FRD. A3: Corresponding postoperative 12 mm horizontal B scan. A4: Postoperative color fundus with cloudy media due to postoperative cataract formation. A5: Postoperative cataract-free En face view depicting superficial retinal abnormalities located inferior to the fovea. A6: Corresponding postoperative Superficial Vascular Plexus (SVP) with vascular deficiencies in the VD and flow perfusion index corresponding with the superficial area defects. A7: The corresponding foveal avascular zone looks enlarged and irregular in shape. A8: The quantified corresponding choriocapillaris flow area perfusion index is within the normal range. A9: The long-term postoperative SD-OCT horizontal segmentation scan with the segmentation green line shows thinning of the inner retinal layer on the nasal side of the fovea and corresponding with the reduced distinct flow area in the SVP. The red dots indicate retinal and choroidal vessels. A10: Inner retinal thickness map where regional thinning of the superficial layers of the retina and quantified thickness values in the key to the right are seen. A11: The color overlays on the OCTA image indicate the VD values shown in the key to the right.

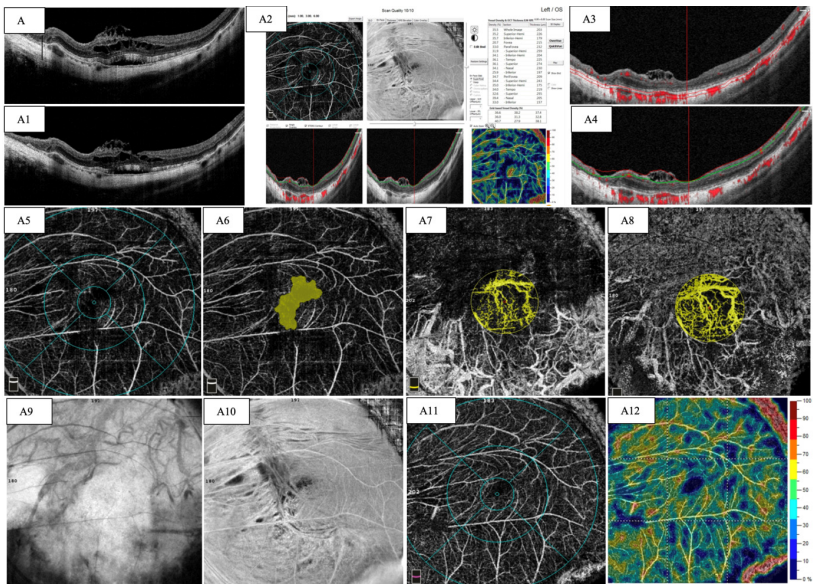

Figure 6: Surgical case 3: A-A1: Preoperative 100 microns apart raster horizontal B scans of a symptomatic highly myopic eye of a 43-year-old female patient with a very complex myopic foveoretinal detachment and severe altered outer retinal layers, there is abundant amount of intraretinal middle layer fluid within the schisis cavities. A2: After an uneventful macular surgery the Superficial Vascular Plexus (SVP) showed quantitative deficiencies according to the ETDRS-like sectors grid overlay, with the table of VD perfusion index values and retinal thickness values seen in this image. A3-A4: Corresponding postoperative SD-OCT horizontal scan depicting residual vitreous hyaloidal remnants with retinal dots representing retinal and choroidal vessels, the green and red segmentation lines showed irregular superficial retinal thinning. A5: Magnified SVP slab with VD perfusion index lower than mean. A6: The foveal avascular zone was quantified as larger than average and irregular qualitatively in shape. A7-A8: Images depicts abnormal quantified areas of choroidal flow with irregular but good perfusion indices (VD and flow index) at the selected subfoveal choriocapillaris flow area. A9-A10: En face images showing diffuse retinal thinning and evident posterior pole deep vessels and inner scleral surface irregularities. A11 deep vascular plexus reveled a normal compensatory vascular flow. A12: The color overlays on the OCTA image indicate the VD perfusion index values shown in the key to the right, whole-macula VD indicated within 3mm × 3mm squares.

DISCUSSION

At the subclinical or clinical level, MF and FRD may be responsible for slowly progressive visual loss and severe visual disturbances in eyes with MTM. Our OCT angiography perfusional findings provided structural and perfusion data from non-surgically and surgically resolved myopic FRD eyes with MTM. The morphologic and vascular perfusion data correlated well with functional changes, which may elucidate the perfusional mechanisms underlying MTM. It is possible that increased compensatory perfusion, as indicated by increased VD, may have a rescue effect in eyes with MF and prevent FRD progression to more advanced stages of this condition, such as myopic macular hole [17].

Our study suggests that early-stage MTM in symptomatic highly myopic patients may benefit from timely well-planned uncomplicated macular surgery. The use of a modified fovea-sparing ILM technique reduced the risk and progression to more advanced stages of MTM [18,19]. In this study, we used two different ILM removal techniques without observing distinct statistically significant differences in the qualitative and quantitative evaluation of postoperative VD perfusion indices between the techniques. Wang et al. [17] described a possible compensatory autoregulatory mechanism in the choroidal perfusion support indicated by increased VD in the choroidal capillary layer that may help maintain the MF and prevent its progression to FRD. In the previous studies, only lower macular sensitivity detected with microperimetry was reported in highly myopic eyes without detachment, suggesting the usefulness of this functional technique for longitudinal surveillance of the retina to predict myopic pathology before vision loss [20]. Our study could not find this compensatory incremental choroidal VD finding at a clinically or statistically significant level. We detected decreased choroidal perfusion in myopic eyes in accordance with the report by Al-Sheikh et al. [21], and enhanced-depth imaging OCT revealed choroidal thinning in the macular region as an age-related degenerative change described in high myopia [11, 22, 23]. The decreased subfoveal choroidal thickness observed in the early stages of MTM may precede the development of retinoschisis. In addition to inner mechanical stretch forces, the etiology of retinoschisis may include poor choroidal support for the health of Müller cells and consequent development of elongated fibrils on the cells.

Some studies have described the role of the Müller cell integrity in traction maculopathies since it is a pathology of the Müller cell cones involving both inner traction from the ILM and outer stretch forces from the PS, as described by Wang et al. [17]. Structural changes in the Müller cells are assumed to occur in eyes with retinoschisis [24]. As the retinoschisis cavities enlarge, mechanical stretch forces may damage Müller cells and affect their function [25]. Therefore, we agree with the hypothetical concept that the Müller cell dysfunction leads to visual impairment in eyes with retinoschisis-type MTM, as Wang et al. stated [17].

Some surgical results have indicated that reorientation of the abnormal architecture of the Müller cell fibrils by releasing traction and resolving the internal/external MF and flattening the myopic FRD is of paramount importance for improving or restoring visual acuity in eyes with the early stage of MTM. As the foveal ILM is a part of the foveal Müller cell fibril, its surgical preservation may prevent further progression to more advanced stages of MTM [18, 19, 26].

We hypothesized that the reduced visual acuity associated with the early stage of MTM is assumed to be the result of foveal distortion rather than the disruption of photoreceptors in MF and photoreceptor disruption plus chronic photoreceptor separation from the RPE in myopic FRD. We hypothesize that this is due to chronic subretinal fluid with a loss of nourishment accompanied by the consequent photoreceptor damage in myopic FRD, which was correlated with the loss of the EZ integrity seen in the preoperative and postoperative structural SD-OCT evaluation but not in healthy highly myopic eyes.

Several studies have correlated choroidal perfusion with VD. In this manner, choroidal perfusion (as reflected in VD) in eyes with advanced-stage MTM (such as MH and MHRD) should not be further temporarily diminished by transoperative perfusional alterations or permanently by compression of the choroid secondary to macular buckling surgery, which may further compress the choroid and further reduce choroidal perfusion [17]. FAZ distortion and area enlargement contribute to decreased VD in MF, and subsequent impairment of visual acuity due to myopic FRD should be corrected by removing the mechanical stretching forces by peeling off the epiretinal membrane, posterior hyaloid, and parafoveolar ILM. In our study and the study by Wang et al. [17], there was a positive correlation between BCVA and mean macular VD in the SVP and the 1 mm selected foveal area of the choroid capillary layer in non-operated eyes with MF/FRD and the fully resolved myopic FRD due to MTM at the end of follow-up; however, no correlation was found in healthy highly myopic eyes in the control group in our study, suggesting that choroidal capillary vascular density flow abnormalities or deficiencies detected by quantifying the choriocapillaris vascular area and reflected in a low value of choroidal thickness itself may not directly affect the vision, but this important hypothetical concept needs further perfusional research.

In a large case series [10], Panozzo and Mercanti concluded that the surgical resolution of vitreoretinal traction during the early stage of myopic FRD would allow re-flattening of the macular center, thus preventing the development of full-thickness MH and emphasizing the high prevalence of an ERM in highly myopic eyes with MF and FRD. However, this large case series lacked both perfusional and qualitative evaluations using fluorescein angiography and quantitative VD evaluation using the AngioVue with OCT angiography as the study by Wang et al. [17] and our study did. Therefore, only the mechanical tractional alteration was hypothesized without addressing the role of possible macular and choroidal perfusional abnormalities. Choroidal perfusion support, indicated by increased VD in the choroid capillary layer may help maintain a stable MF with a low rate of MTM

progression and prevent FRD formation [17]. Al-Sheikh et al. [21] proposed that decreased choroidal perfusion and a lower VD pattern quality in myopic eyes with a reduced whole-macula VD, consequently with lower macular perfusion, may result from mechanical stretch forces induced by eyeball elongation.

Quantitatively, a VD evaluation to assess macular microcirculation is of paramount clinical importance as even mild microcirculation changes may lead to pathological changes with quality vision repercussions [27]. Small-vessel changes with lower VD values have been demonstrated in multiple retinal vascular diseases, including diabetic retinopathy, macular telangiectasia, and radiation retinopathy [28-30].

In this study, owing to the reliability of the reproducibility of OCT angiography quantitative VD evaluation, we were able to report a reliable statistical analysis evaluation. Our multivariate regression analysis showed that BCVA was positively correlated with the choriocapillaris flow area and negatively correlated with CSFT (analysis done with BCVA logMAR units showing a negative correlation with the choriocapillaris flow area and a positive correlation with CSFT). In the surgical group, the change in BCVA before versus after surgery was analyzed using 14 biomarkers, but none was statistically significant. The results also revealed that structural defects in the EZ were positively correlated with the superficial FAZ area and ELM defects. Similarly, structural defects in ELM were positively correlated with EZ defects and negatively correlated with deep whole macular VD. Thus, we have reported new information regarding the statistical analysis of normal-range vessel changes in normal emmetropic eyes, healthy highly myopic eyes, and non-operated eyes with MF and FRD and in eyes with fully surgically resolved myopic FRD. However, this perfusional information and data need to be validated in further research. Our results indicate statistically non-significant changes in macular perfusion between the control groups and significant differences in the quantitative VD evaluation between the study groups. However, the data were highly significant when the microcirculation of the macula through the quantitative VD evaluation value was compared across groups; the difference between healthy eyes, MF/FRD non-operated, and surgically resolved myopic FRD eyes was highly significant ($p<0.001$). These findings allowed us to speculate the interrelation between tractional mechanisms and perfusional mechanisms without concluding the physiopathogenic order.

Similar to the study by You et al. [31], we found that the measurements of paracentral subfields were not affected by the FAZ area and that FAZ area had a lesser effect on the complete macular area evaluation. This result allowed us to conclude that the quantitative evaluation of macular VD in the paracentral macular area is as reliable as measuring the entire vascular macular area. Peng et al. [32] also speculated that the upregulated local cytokine production drove the resolution of myopic FRD after fovea-sparing ILM removal, thus, implicating the vascular microenvironment together with alterations in microcirculation permeability in patients with MTM. Our study provides insight into the early stages of MTM, indicating that there are factors at the microcirculation level in its tractional pathogenesis.

We acknowledge the inherent limitations of our retrospective series, including the relatively small number of eyes. This was primarily related to the strict exclusion criteria we applied to limit our study to non-surgically and successfully surgically corrected eyes in the early stage of MTM in a long-term assessment. The study lacks a serial or longitudinal data analysis. However, it has the benefits of SD-OCT and OCT angiography long-term finding correlations and includes a quantitative perfusional changes evaluation. We anticipate that the scientific retina community will appreciate our findings due to the sparsity of published material on perfused macular assessment in the early stage of MTM and the postoperative perfusion status of the macula in highly myopic eyes.

CONCLUSION

Further investigations, including further perfusional and histopathologic studies, are necessary to confirm the role of *in vivo* perfusional macular mechanisms in the pathogenesis of MF/FRD due to MTM. These studies would help elucidate the role of microvascular perfusion mechanisms in maintaining the Müller cell integrity in traction maculopathies, as MTM is a pathology of the Müller cell cones involving the inner traction from the ILM and the outer stretch forces from the PS. Thus, perfusional mechanisms must be investigated in detail in the future.

DECLARATIONS

Acknowledgments

We express our deep appreciation to the technical staff of the Retina Service of the three participating institutions located in Mexico City, Mexico.

Funding

No funding or grant support was received for this study.

Conflict of interest

The authors declare no conflicts of interest.

Availability of data and materials

Photos, composite figures, datasets, and laboratory studies supporting the findings of this study may be released upon written application to the Photographic Laboratory and Clinical Archives Department at the Institute of Ophthalmology Fundacíon Conde de Valenciana (non-profit organization), Chimalpopoca 14, Colonia Obrera, Mexico City, Mexico 06800, and the corresponding author upon request.

Code availability

Not applicable

Authors' contributions

All authors contributed to the study conception and design. The surgeries were performed by Miguel A. Quiroz-Reyes. Material preparation, data collection, and analysis were performed by

Miguel A. Quiroz-Reyes, Erick A. Quiroz-Gonzalez, Jorge G. Morales-Navarro, Miguel A. Quiroz-Gonzalez, Boris Moreno-Andrade, Mario Carranza-Casas, Ana L. Diazceballos-Garcia, Alejandra Nieto-Jordan, Virgilio Lima-Gomez, and Federico Graue-Wiechers. The first and main draft of the manuscript was written by Miguel A. Quiroz-Reyes, and all authors commented on the previous versions of the manuscript. All authors have read and approved the final manuscript for publication.

Ethics approval

All procedures performed in this study involving human participants were done so in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This multicenter retrospective study received full ethical approval from the research ethics board and was approved by the institutional review committees and the teaching departments of the three institutions enrolled (no reference number is provided for retrospective studies by these institutions). Written informed consent was obtained from all patients in accordance with institutional guidelines.

Consent to participate

Informed consent was obtained from all participants included in the study.

Consent for publication

The authors affirm that the participants provided informed consent for the publication of all images figures as well as images in the online resources, if any.

REFERENCES

1. Naidoo KS, Fricke TR, Frick KD, Jong M, Naduvilath TJ, Resnikoff S, et al. Potential lost productivity resulting from the global burden of myopia: systematic review, meta-analysis, and modeling. Ophthalmology. 2019;126(3):338-346.
2. Ohno-Matsui K, Wu PC, Yamashiro K, Vutipongsatorn K, Fang Y, Cheung CMG, et al. IMI Pathologic Myopia. Invest Ophthalmol Vis Sci. 2021;62(5):5.
3. Parolini B, Palmieri M, Finzi A, Besozzi G, Frisina R. Myopic traction maculopathy: a new perspective on classification and management. Asia-Pac J Ophthalmol2021;10(1):49-59.
4. Parolini B, Palmieri M, Finzi A, Besozzi G, Lucente A, Nava U, et al. The new myopic traction maculopathy staging system. Eur J Ophthalmol.2021;31(3):1299-1312.
5. Iwasaki M, Miyamoto H, Okushiba U, Imaizumi H. Fovea-sparing internal limiting membrane peeling versus complete internal limiting membrane peeling for myopic traction maculopathy. Jpn J Ophthalmol. 2020;64(1):13-21.
6. Frisina R, Gius I, Palmieri M, Finzi A, Tozzi L, Parolini B. Myopic traction maculopathy: diagnostic and management strategies. Clin Ophthalmol. 2020;14:3699.
7. Shimada N, Tanaka Y, Tokoro T, Ohno-Matsui K. Natural course of myopic traction maculopathy and factors associated with progression or resolution. Am J Ophthalmol. 2013;156(5):948-957.
8. Shimada N, Ohno-Matsui K, Baba T, Futagami S, Tokoro T, Mochizuki M. Natural course of macular retinoschisis in highly myopic eyes without macular hole or retinal detachment. Am J Ophthalmol. 2006;142(3):497-500.
9. Ikuno Y, Tano Y. Early macular holes with retinoschisis in highly myopic eyes. Am J Ophthalmol. 2003;136(4):741-744.
10. Panozzo G, Mercanti A. Optical coherence tomography findings in myopic traction maculopathy. Arch Ophthalmol. 2004;122(10):1455-1460.
11. Margolis R, Spaide RF. A pilot study of enhanced depth imaging optical coherence tomography of the choroid in normal eyes. Am J Ophthalmol. 2009;147(5):811-815.
12. Ho AC, Yannuzzi LA, Guyer DR, Slakter JS, Sorenson JA, Orlock DA. Intraretinal leakage of indocyanine green dye. Ophthalmology. 1994;101(3):534-541.
13. Hwang TS, Zhang M, Bhavsar K, Zhang X, Campbell JP, Lin P, et al. Visualization of 3 distinct retinal plexuses by projection-resolved optical coherence tomography angiography in diabetic retinopathy. JAMA Ophthalmol. 2016;134(12):1411-1419.
14. Ruiz-Medrano J, Flores-Moreno I, Ohno-Matsui K, Cheung CM, Silva R, Ruiz-Moreno JM. Validation of the recently developed atn classification and grading system for myopic maculopathy. Retina.2020;40(11):2113.
15. Klufas MA, Phasukkijwatana N, Iafe NA, Prasad PS, Agarwal A, Gupta V, et al. Optical coherence tomography angiography reveals choriocapillaris flow reduction in placoid chorioretinitis. Ophthalmol Retina. 2017;1(1):77-91.
16. Kuehlewein L, Bansal M, Lenis TL, Iafe NA, Sadda SR, Bonini Filho MA, et al. Optical coherence tomography angiography of type 1 neovascularization in age-related macular degeneration. Am J Ophthalmol. 2015;160(4):739-748.
17. Wang SW, Hung KC, Tsai CY, Chen MS, Ho TC. Myopic traction maculopathy biomarkers on optical coherence tomography angiography—An overlooked mechanism of visual acuity correction in myopic eyes. Eye. 2019;33(8):1305-1313.
18. Shimada N, Sugamoto Y, Ogawa M, Takase H, Ohno-Matsui K. Fovea-sparing internal limiting membrane peeling for myopic traction maculopathy. Am J Ophthalmol. 2012;154(4):693-701.
19. Shiraki N, Wakabayashi T, Ikuno Y, Matsumura N, Sato S, Sakaguchi H, et al. Fovea-sparing versus standard internal limiting membrane peeling for myopic traction maculopathy: a study of 102 consecutive cases. Ophthalmol Retina. 2020;4(12):1170-1180.
20. Wong QY, Dan YS, Yu DJ, Hoang QV, Wong CW. A microperimetric evaluation of macular function in highly myopic eyes with myopic macular degeneration. InInvestigative Ophthalmology & Visual Science 2020. 61(7).
21. Al-Sheikh M, Phasukkijwatana N, Dolz-Marco R, Rahimi M, Iafe NA, Freund KB, et al. Quantitative OCT angiography of the retinal microvasculature and the choriocapillaris in myopic eyes. Investig. Ophthalmol. Vis Sci. 2017;58(4):2063-2069.
22. Gaucher D, Haouchine B, Tadayoni R, Massin P, Erginay A, Benhamou N, et al. Long-term follow-up of high myopic foveoschisis: Natural course and surgical outcome. Am J Ophthalmol. 2007;143(3):455-462.

23. Sebag J. Anomalous posterior vitreous detachment: A unifying concept in vitreo-retinal disease. Graefes Arch. Clin. Exp. Ophthalmol. 2004;242(8):690-698.

24. Tang J, Rivers MB, Moshfeghi AA, Flynn HW, Chan CC. Pathology of macular foveoschisis associated with degenerative myopia. J Ophthalmol. 2010.

25. Park S, Lee YJ. Nano-mechanical compliance of müller cells investigated by atomic force microscopy. Int J Biol Sci. 2013;9(7):702.

26. Ho TC, Yang CM, Huang JS, Yang CH, Yeh PT, Chen TC, et al. Long-term outcome of foveolar internal limiting membrane nonpeeling for myopic traction maculopathy. Retina. 2014;34(9):1833-1840.

27. Yu DY, Cringle SJ. Oxygen distribution and consumption within the retina in vascularised and avascular retinas and in animal models of retinal disease. Prog Retin Eye Res.2001;20(2):175-208.

28. Chin EK, Kim DY, Hunter AA, Pilli S, Wilson M, Zawadzki RJ, et al. Staging of macular telangiectasia: Power-Doppler optical coherence tomography and macular pigment optical density. Investig Ophthalmol Vis Sci. 2013;54(7):4459-4470.

29. Veverka KK, AbouChehade JE, Iezzi Jr R, Pulido JS. Noninvasive grading of radiation retinopathy: The use of optical coherence tomography angiography. Retina. 2015;35(11):2400-2410.

30. You QS, Freeman WR, Weinreb RN, Zangwill L, Manalastas PI, Saunders LJ, et al. Reproducibility of vessel density measurement with optical coherence tomography angiography in eyes with and without retinopathy. Retina.2017;37(8):1475.

31. Peng M, Wei Y, Zhang Z, Zhang T, Qiu S, Fang D, et al. Increased levels of DKK1 in vitreous fluid of patients with pathological myopia and the correlation between DKK1 levels and axial length. Curr Eye Res. 2020;45(1):104-110.