• Clinical Research •

Epiretinal membrane related vascular changes in diabetic eyes evaluated with optical coherence tomography angiography

Umay Güvenç, Güner Üney, Nurten Ünlü, Mehmet Akif Acar, Dicle Hazırolan, Özlem Candan

Ankara Training and Research Hospital Ophthalmology Department, Ankara 06800, Türkiye

Correspondence to: Umay Güvenç. Güzeltepe mah. 747. sk. Park Vadi Evleri A3 Blok No:51 Çankaya/Ankara 06800, Türkiye. umay.guvenc@gmail.com

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Abstract

• **AIM:** To evaluate the retinochoroidal microvascular circulation and anatomical structure of diabetic and non-diabetic patients with epiretinal membrane (ERM) with the help of optical coherence tomography angiography (OCT-A) and compare them with healthy control subjects.

• **METHODS:** In this prospective, cross-sectional study, a total of 165 eyes were evaluated, including 50 eyes of patients with diabetic ERM, 54 eyes of idiopathic ERM (iERM) patients, and 61 eyes of healthy controls. Macula and disc angiography was performed by OCT-A. Macular vessel density (VD) ratio was evaluated by dividing the VD of the foveal region by the VD of the parafoveal region. Statistical calculations were evaluated at the 95% confidence interval.

• **RESULTS:** Macula superficial VD values of ERM cases were lower than that in the control group, while foveal VD was higher in ERM cases. Macula deep VD values of ERM cases were lower in all quadrants, except the fovea. The width of the foveal avascular zone (FAZ) area was significantly lower in the ERM groups, and the FAZ width was lowest in iERM group. Macula superficial VD ratio was significantly higher in the ERM groups, but there was no significant difference between ERM groups. Macula deep VD ratio was significantly higher in the iERM group than in the control group.

• **CONCLUSION:** Diabetic and idiopathic ERMs differ in their mechanism of formation and clinical presentation, as well as their effect on retinal vascular structures. If the relationship of increase of retinal thickness with vascular integrity can be demonstrated with OCT-A, then, OCT-A can be used as a guide for ERM prognosis.

• **KEYWORDS:** diabetic macular edema; epiretinal membrane; macula vessel density ratio; optical coherence tomography angiography

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INTRODUCTION

Epiretinal membrane (ERM) is defined as the pre-retinal proliferation of extracellular matrix associated myofibroblastic cells and its prevalence is 9.1%[1]. The term of idiopathic epiretinal membrane (iERM) is used for ERMs seen in the absence of any underlying ocular anomaly[2]. The rate of posterior vitreous detachment (PVD) in iERMs is 78%-95%, suggesting the importance of PVD in the development of ERM[3-4]. Secondary ERM is defined as an ERM that accompanies an underlying ocular disease. The rate of secondary ERM is 32.3% among all ERMs, and the most common causes are previous cataract surgery, diabetic retinopathy, and retinal vein occlusion[1].

ERM formation causes anteroposterior and tangential forces in the retina. Anteroposterior forces create vertical traction and are manifested by retinal thickening, which can be easily detected with optical coherence tomography (OCT). In addition, this causes displacement of vascular structures through tangential forces that drag the fovea from its original position. Tangential forces and their vascular distortion are relatively difficult to detect and major causes of metamorphopsia[5].

In addition to mechanical traction forces, diabetic macular edema (DME) is the other component of increased foveal thickness in diabetic ERM patients. DME is a multifactorial and complex condition that mainly results from the accumulation of fluid and serum macromolecules in the intercellular space as a result of deterioration in the blood retina barrier[6]. Many studies have shown that ERM is much more common in eyes with DME. High glucose levels can

alter the structure and function of the vitreoretinal interface, leading to the accumulation of advanced glycosylation end-products. This explains the development of abnormal PVD in diabetic individuals, even at a young age[7].

Although it is easy to detect retinal thickening caused by vertical forces with the help of OCT, it is not so easy to detect vascular distortion caused by tangential forces. For this purpose, the use of imaging techniques such as color fundus photography, confocal scanning infrared ophthalmoscopy, and red-free and fundus autofluorescence imaging has been reported[8].

Recent technological advances have led to the emergence of optical coherence tomography angiography (OCT-A), which represents a novel imaging modality that allows for en-face retinal vessel visualization without dye injection[9]. OCT-A can show secondary causes of ERM such as retinal vascular diseases (diabetic retinopathy and vein occlusion), retinal vasculitis, and vascular tumors and is effective in evaluating the damage caused by the tangential and vertical forces of ERMs on macular vascular structures.

The aim of our study is to evaluate, non-invasively and depth-selectively, the extent of foveal vascular displacement in patients with diabetic and idiopathic ERM (iERM) using OCT-A and to compare this findings from healthy control subjects.

SUBJECTS AND METHODS

Ethical Approval Approval for the study was obtained from the ethics committee of Health Sciences University, Ankara Training and Research Hospital by approval number E-19-170 on 26/06/2020. Informed consent was obtained from each study patient and control subject. All procedures adhered to the tenets of the Declaration of Helsinki.

Subjects A total of 165 eyes, including 50 eyes of diabetic ERM patients, 54 eyes of iERM patients, and 61 eyes of healthy controls were included in this prospective, cross-sectional study. Data collection was completed between December 2020 and May 2021. We enrolled participants who applied to the Ankara SUAM Ophthalmology Polyclinic. The study included patients who had complaints of blurred vision, low vision, metamorphopsia, or asymptomatic ERM during routine examination. The patients were categorized into different groups based on the underlying condition. The iERM group included individuals who had ERM without any known disease, while the diabetic ERM group included individuals with secondary ERM caused by diabetes mellitus. Patients with non-proliferative diabetic retinopathy, which is characterized by microaneurysms, hard exudates, and non-diffuse retinal hemorrhages, were included in the diabetic group. To establish a baseline, a control group of healthy individuals who were similar in age to the patients was also included in the study. We excluded those with glaucoma, keratoconus, uveitis, strabismus, amblyopia, proliferative diabetic retinopathy, hypertension and other systemic diseases, contact lens wear, ocular trauma, ocular surgery, and those with spherical and cylindrical refractive errors of more than 2 diopters.

Data Collection Objective refraction measurements were made with the Huvitz MRK-3100 auto refractometer device (Huvitz, Korea). The best-corrected visual acuity (BCVA) was measured using the Snellen chart. Intraocular pressure measurements were made with Goldmann applanation tonometry. Pupil dilation was achieved by a single drop of tropicamide 0.5% (Tropamid® 0.5%, Bilim Ilaç San. Ve Tic. A.Ş., Turkey) after biomicroscopic anterior segment examination. Detailed fundus examination was performed following pupillary dilatation. After a 15-min resting period, spectral domain OCT was performed with an Heidelberg Spectralis HRA+OCT device (Heidelberg Engineering, Heidelberg, Germany), and macula and peripapillary retinal nerve fiber layer thicknesses (RNFLT) values were obtained. An OCT-A AngioVue device (RTVue-XR, Fremont, California, USA; software version 2017.1.0.151) was used on all participants. The patients underwent macular 6×6 mm^2 retinal angiography (Figure 1).

The non-flow area was calculated from superficial capillary plexus (SCP), and foveal avascular zone (FAZ), FAZ circumference acircularity index, and foveal density were calculated automatically from all retinal layers. (Figure 2).

The area with a radius of 1 mm was used as the basis for the choriocapillaris flow area (Figure 3). Tangential forces of ERM are known to cause vessel shift from the parafoveal region into the foveal region. Therefore, we propose a macular vessel density ratio (MVR), dividing the vessel density (VD) of the foveal region (VDfo) by the VD of the parafoveal region (VDp) in order to quantify the extent of change in foveal capillary architecture (MVR=VDfo/VDp). In this manner, we determined the MVR in the superficial and the deep slabs. Choroidal images were taken using the enhanced high definition (HD) line module, and choroidal thickness values were analyzed manually. Signal strength above 60 was accepted. The choroidal thickness was measured manually from 3 separate points: foveal, 1500 μm temporal from the foveal center and 1500 μm nasal. Measurements were made based on the total choroidal thickness from the retinal pigment epithelium RPE to the hyperreflective scleral wall.

Age, gender, the presence of diabetes mellitus and other diseases, and use of insulin or oral antidiabetic agents, were noted.

Statistical Analysis Data analyses were performed using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA). Whether distribution of continuous variables was

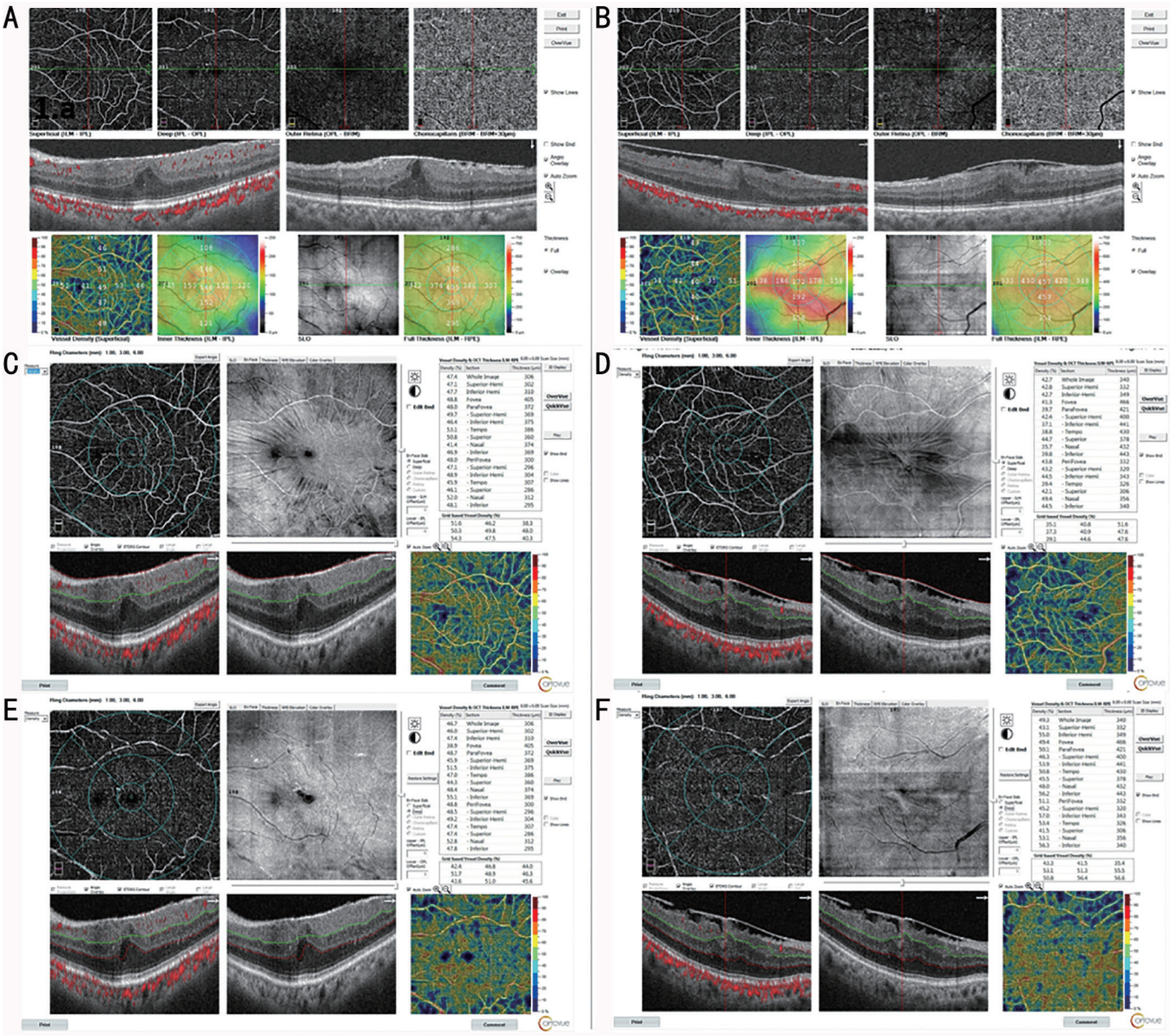

Figure 1 Angio retina scan (6×6 mm^2) The fovea of the left eye of a diabetic epiretinal membrane (ERM; A), right eye of an idiopathic ERM (B). Macula superficial vessel density (MSVD) values of the left eye of a diabetic ERM (C), right eye of an idiopathic ERM (D). Macula deep vessel density (MDVD) values of the left eye of a diabetic ERM (E), right eye of an idiopathic ERM (F).

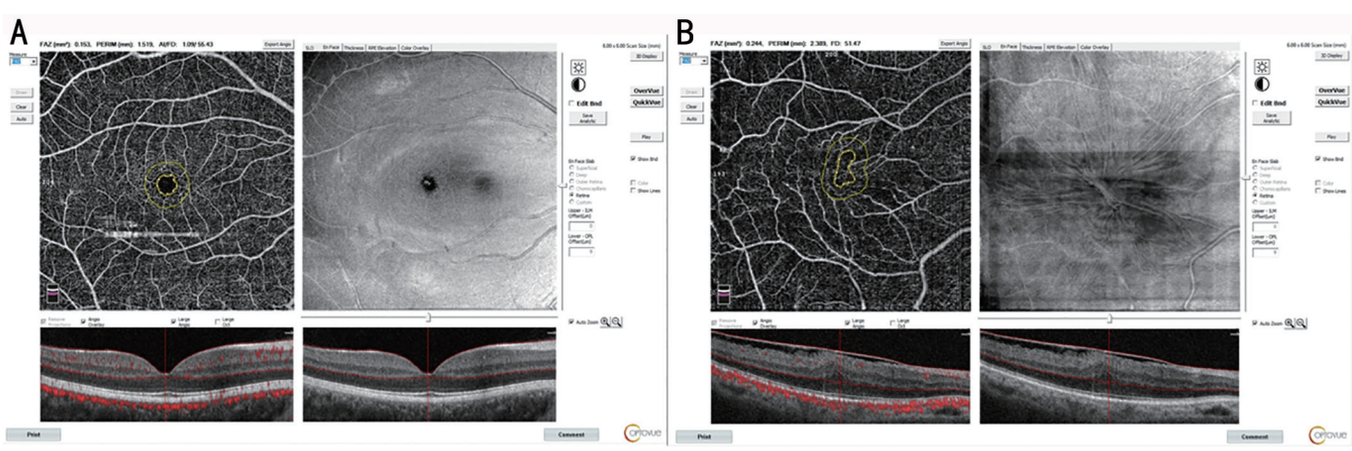

Figure 2 Angio retina scan 6×6 mm^2 is centered on the right fovea at the level of the superficial retinal networks A: Healthy control; B: Idiopathic epiretinal membrane on with a prevelant distortion of the foveal avascular zone area.

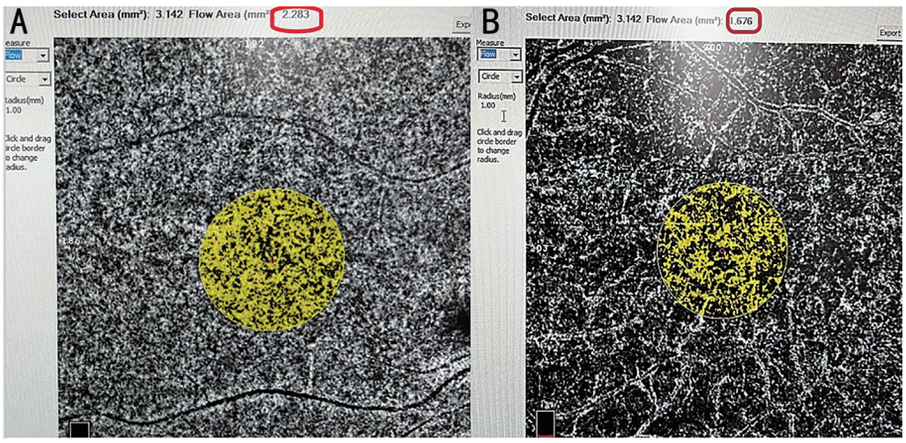

Figure 3 Optical coherence tomography angiography choriocapillaris flow area measurements A: An idiopathic epiretinal membrane patient; B: A diabetic epiretinal membrane patient.

normal or not was determined by Kolmogorov-Smirnov test. The Levene test was used for the evaluation of homogeneity of variances. Unless specified continuous data were described as mean±standard deviation (SD) for normal distributions, and median (first quarter-third quarter) for skewed distributions. Categorical data were described as number of cases (%). Categorical variables were compared using Pearson's Chi-square test or Fisher's exact test. While the differences in normally distributed variables among more than two independent groups were analysed by One-way ANOVA tests, Kruskal-Wallis tests were applied for comparisons of data that were not normally distributed. When the *P* values from the one-way ANOVA or Kruskal-Wallis tests were statistically significant, post-hoc Bonferroni or Conover-Iman multiple comparison tests were used to show which groups differed from which. The relationship between continuous variables was evaluated with Pearson or Spearman correlation analyses and a *P* value <0.05 was accepted as the significance level in all statistical analyses.

RESULTS

A total of 165 eyes of 165 participants were examined. Participants were analyzed in three categories: 50 diabetic ERM patients, 54 iERM patients, and 61 controls. The mean age of the participants was 68.10±6.81y and there was no significant difference between the groups (*P*>0.05).

The mean duration of diabetes in diabetic ERM patients was 15.62±7.60y. In the diabetic group, none of them had complications related to diabetes such as proliferative retinopathy or nephropathy. BCVA values of ERM patients were statistically significantly lower than those in the control group (*P*<0.001). There was no statistically significant difference between the groups in terms of intraocular pressure values (*P*>0.05).

In the comparison of macula superficial VD, ERM cases were significantly lower in all quadrants compared to the control group, while foveal vessel density was higher in ERM cases. There was no significant difference between the diabetic and idiopathic ERM groups. However, it was observed that the superficial VD were lower in all quadrants in the diabetic ERM group (Table 1).

In the comparison of macula deep VD, the VD of ERM cases significantly lower in all quadrants, except the fovea, compared to the control group, while no significant difference was found between the ERM groups. No significant difference was observed among the three groups in terms of foveal deep VD (Table 2).

The width of the FAZ area was significantly lower in the ERM groups compared to the control group. Although there was no statistically significant difference in FAZ area between ERM groups, the FAZ width was the lowest in the iERM group (Table 3). Choriocapillaris flow area was significantly lower in the diabetic ERM group compared to the other groups (Figure 3).

The retinal thickness values in all quadrants of the ERM groups were significantly higher than in the control group. No significant difference was observed between ERM groups. There was no significant difference between the three groups in terms of choroidal thickness values (Table 4).

MVR was evaluated for SCP and deep capillary plexus (DCP) and compared between groups, it was observed that macula superficial vascular density ratio was significantly higher in ERM groups compared to the control group. However, there was no significant difference between ERM groups. Macula deep vessel density ratio was significantly higher in the iERM group compared to the control group (Table 5).

In the correlation analysis of superficial and deep VD with retinal thickness values and BCVA, a weakly positive correlation was found between BCVA and superficial VD of superior hemisphere and deep VD of macula in the diabetic ERM group (r=0.281, P=0.048; r=0.340, P=0.016).

In the iERM group, a moderately positive correlation was observed between both superficial and deep VD of fovea and

Table 1 Comparison of diabetic and idiophatic ERM cases and control group in terms of macula superficial vessel density

MSVD (%)	d-ERM (*n*=50)	i-ERM (*n*=54)	Control (*n*=61)	*P*
Ti	40.65 (38.10-45.50)	42.85 (40.00-46.00)	47.70 (44.90-49.70)	<0.001[b,c]
SH	41.94±5.10	42.91±4.70	46.52±3.89	<0.001[b,c]
IH	41.35 (38.00-45.40)	43.35 (40.20-46.70)	47.60 (45.60-49.90)	<0.001[b,c]
F	26.06±11.52	26.54±11.01	18.97±8.36	<0.001[b,c]
P	41.20 (35.80-46.20)	42.90 (37.50-47.00)	49.00 (46.00-51.60)	<0.001[b,c]
PSH	40.60 (34.60-45.80)	42.10 (37.60-48.90)	50.20 (46.00-51.90)	<0.001[b,c]
PIH	41.45 (36.60-45.70)	43.90 (36.70-48.10)	48.60 (44.50-51.80)	<0.001[b,c]
PT	43.30 (39.50-46.50)	43.10 (39.20-48.80)	50.40 (47.30-52.90)	<0.001[b,c]
PS	42.50 (37.90-48.00)	44.00 (38.70-49.70)	50.80 (46.20-53.80)	<0.001[b,c]
PN	38.25 (31.80-44.80)	39.95 (33.20-45.10)	45.20 (43.40-49.00)	<0.001[b,c]
PI	42.20 (36.40-46.90)	45.10 (37.10-49.50)	49.50 (44.70-53.00)	<0.001[b,c]
PE	42.25 (39.60-46.30)	44.70 (40.70-48.00)	48.50 (45.70-50.80)	<0.001[b,c]
PESH	42.92±5.19	44.12±5.10	47.23±4.06	<0.001[b,c]
PEIH	42.35 (39.60-46.90)	44.80 (40.30-47.90)	48.80 (46.50-51.30)	<0.001[b,c]
PET	36.60 (33.60-43.80)	39.55 (33.40-44.00)	44.10 (41.10-46.40)	<0.001[b,c]
PES	42.82±6.06	43.96±6.42	46.96±4.87	<0.001[b,c]
PEN	47.20 (45.10-51.30)	49.40 (46.80-53.10)	53.30 (49.45-55.10)	<0.001[b,c]
PEI	43.10 (40.70-45.80)	45.15 (40.60-49.30)	48.50 (45.40-51.10)	<0.001[b,c]

Conover-Iman or Bonferroni tests were performed for the binary comparisons among the groups and, the *P* value was set at 0.05. Significant differences were found between: b: dERM *vs* control; c: iERM *vs* control. d-ERM: Diabetic epiretinal membrane; i-ERM: Idiopathic epiretinal membrane; MSVD: Macula superficial vessel densitiy; Ti: Total image; SH: Superior hemisphere; IH: İnferior hemisphere; F: Fovea; P: Parafovea; PSH: Parafoveal superior hemisphere; PIH: Parafoveal inferior hemisphere; PT: Parafoveal temporal; PS: Parafoveal superior; PN: Parafoveal nasal; PI: Parafoveal inferior; PE: Perifoveal; PESH: Perifoveal superior hemisphere; PEIH: Perifoveal inferior hemisphere; PET: Perifoveal temporal; PES: Perifoveal superior; PEN: Perifoveal nasal; PEI: Perifoveal inferior.

Table 2 Comparison of diabetic and idiophatic ERM cases and control group in terms of macula deep vessel density

MDVD (%)	d-ERM (*n*=50)	i-ERM (*n*=54)	Control (*n*=61)	*P*
Ti	41.08±4.87	40.59±5.52	44.86±4.55	<0.001[b,c]
SH	40.73±5.79	40.29±5.45	44.44±4.68	<0.001[b,c]
IH	41.26±4.71	40.83±6.27	45.29±5.01	<0.001[b,c]
F	34.18±8.80	36.95±11.24	34.93±8.78	0.313
P	44.91±6.07	45.31±6.63	50.17±3.63	<0.001[b,c]
PSH	44.44±8.55	45.69±7.41	50.50±3.94	<0.001[b,c]
PIH	45.29±5.89	44.87±7.54	49.79±3.92	<0.001[b,c]
PT	47.08±7.53	47.04±8.91	51.89±4.32	<0.001[b,c]
PS	44.30 (41.00-51.40)	45.50 (41.30-51.00)	50.10 (47.60-52.00)	<0.001[b,c]
PN	44.40 (41.10-49.20)	44.35 (38.90-50.70)	49.50 (46.70-52.20)	<0.001[b,c]
PI	45.39±7.14	44.33±8.53	49.06±4.56	0.001[b,c]
PE	42.00±5.18	40.89±6.37	45.70±5.07	<0.001[b,c]
PESH	41.68±6.24	40.87±6.78	45.38±5.27	<0.001[b,c]
PEIH	42.24±4.99	40.83±6.97	46.03±5.55	<0.001[b,c]
PET	45.75 (41.10-49.80)	46.70 (40.70-50.50)	50.10 (46.00-52.80)	<0.001[b,c]
PES	41.00±6.43	39.71±7.88	43.71±6.01	0.007[c]
PEN	40.10 (37.80-44.60)	38.25 (29.90-44.20)	44.20 (41.10-47.10)	<0.001[b,c]
PEI	41.52±5.41	39.89±7.46	45.41±6.11	<0.001[b,c]

Conover-Iman or Bonferroni tests were performed for the binary comparisons among the groups and, the *P* value was set at 0.05. Significant differences were found between: b: dERM *vs* control; c: iERM *vs* control. d-ERM: Diabetic epiretinal membrane; i-ERM: Idiopathic epiretinal membrane; MDVD: Macula deep vessel densitiy; Ti: Total image; SH: Superior hemisphere; IH: İnferior hemisphere; F: Fovea; P: Parafovea; PSH: Parafoveal superior hemisphere; PIH: Parafoveal inferior hemisphere; PT: Parafoveal temporal; PS: Parafoveal superior; PN: Parafoveal nasal; PI: Parafoveal inferior; PE: Perifoveal; PESH: Perifoveal superior hemisphere; PEIH: Perifoveal inferior hemisphere; PET: Perifoveal temporal; PES: Perifoveal superior; PEN: Perifoveal nasal; PEI: Perifoveal inferior.

Table 3 Comparison of diabetic and idiopathic ERM cases and control group in terms of FAZ and related parameters

Parametres	d-ERM (*n*=50)	i-ERM (*n*=54)	Control (*n*=61)	*P*
FAZ	0.23 (0.12-0.30)	0.19 (0.10-0.36)	0.28 (0.23-0.36)	0.010[b,c]
AI	1.12 (1.10-1.17)	1.12 (1.09-1.18)	1.10 (1.08-1.13)	0.054
FLOW-R	0.88 (0.63-1.29)	1.33 (0.84-1.59)	0.82 (0.53-1.18)	0.002[c]
FLOW-CC	1.87 (1.78-1.98)	2.02 (1.93-2.15)	2.11 (2.03-2.20)	<0.001[a,b]
NON FLOW	0.55 (0.28-0.86)	0.47 (0.23-0.79)	0.52 (0.44-0.67)	0.495

Conover-Iman or Bonferroni tests were performed for the binary comparisons among the groups and, the *P* value was set at 0.05. Significant differences were found between: a: dERM *vs* iERM; b: dERM *vs* control; c: iERM *vs* control. d-ERM: Diabetic epiretinal membrane; i-ERM: Idiopathic epiretinal membrane; FAZ: Foveal avascular zone; AI: Foveal avascular zone circumference acircularity index; FLOW-R: Retinal flow area; FLOW-CC: Choriocapillaris flow area; NON FLOW: Non-flow area.

Table 4 Comparison of diabetic and idiopathic ERM cases and control group in terms of retinal and choroidal thickness values

Retinal and choroidal thickness (μm)	d-ERM (*n*=50)	i-ERM (*n*=54)	Control (*n*=61)	*P*
TT	296.50 (283.00-325.00)	298.00 (280.00-315.00)	281.00 (273.00-291.00)	<0.001[b,c]
SHT	297.00 (283.00-317.00)	299.50 (281.00-317.00)	282.00 (274.00-291.00)	<0.001[b,c]
IHT	292.50 (283.00-316.00)	296.00 (276.00-314.00)	281.00 (271.00-288.00)	<0.001[b,c]
FT	336.50 (281.00-376.00)	340.00 (280.00-398.00)	250.00 (241.00-271.00)	<0.001[b,c]
PT	344.50 (328.00-376.00)	346.00 (323.00-380.00)	321.00 (314.00-333.00)	<0.001[b,c]
PSHT	354.18±42.58	354.61±42.85	322.50±14.86	<0.001[b,c]
PIHT	338.00 (322.00-372.00)	342.50 (323.00-369.00)	321.50 (314.00-334.50)	<0.001[b,c]
PTT	354.98±46.09	349.78±53.12	314.80±14.18	<0.001[b,c]
PST	354.30±45.88	356.13±45.57	326.70±18.22	<0.001[b,c]
PNT	352.92±42.71	354.46±48.84	326.07±15.03	<0.001[b,c]
PIT	338.00 (314.00-369.00)	349.00 (324.00-369.00)	321.50 (315.50-337.50)	0.001[b,c]
PET	297.00 (282.00-318.00)	295.50 (277.00-315.00)	278.50 (270.00-287.50)	<0.001[b,c]
PESHT	297.00 (284.00-324.00)	296.00 (279.00-316.00)	280.50 (272.00-290.50)	<0.001[b,c]
PEIHT	292.00 (281.00-317.00)	291.00 (272.00-311.00)	276.50 (267.00-284.00)	<0.001[b,c]
PETT	295.00 (273.00-325.00)	287.00 (267.00-311.00)	265.00 (257.00-279.00)	<0.001[b,c]
PEST	290.00 (279.00-320.00)	294.00 (277.00-310.00)	281.00 (271.00-289.50)	<0.001[b,c]
PENT	316.47±33.09	310.33±35.02	296.15±16.81	0.001[b,c]
PEIT	285.00 (270.00-305.00)	282.00 (263.00-301.00)	270.50 (262.00-277.50)	0.001[b,c]
C-T	290.50 (278.00-303.00)	274.00 (262.50-304.00)	300.00 (300.00-304.00)	0.490
C-F	335.00 (315.00-355.00)	304.00 (301.50-347.50)	360.00 (360.00-364.00)	0.284
C-N	264.00 (244.00-284.00)	263.50 (246.50-290.50)	260.00 (260.00-270.00)	0.999

Conover-Iman or Bonferroni tests were performed for the binary comparisons among the groups and, the *P* value was set at 0.05. Significant differences were found between: b: dERM *vs* control; c: iERM *vs* control. d-ERM: Diabetic epiretinal membrane; i-ERM: Idiopathic epiretinal membrane; TT: Total macular thickness, SHT: Macula superior hemisphere thickness; IH: Macula inferior hemisphere thickness; FT: Foveal retinal thickness; PT: Parafoveal retinal thickness; PSHT: Parafoveal superior hemisphere retinal thickness; PIHT: Parafoveal inferior hemisphere retinal thickness; PST: Parafoveal superior retinal thickness; PTT: Parafoveal temporal retinal thickness; PIT: Parafoveal inferior retinal thickness; PNT: Parafoveal nasal retinal thickness; PET: Perifoveal retinal thickness; PESHT: Perifoveal superior hemisphere retinal thickness; PEIHT: Perifoveal inferior hemisphere retinal thickness; PEST: Perifoveal superior retinal thickness; PETT: Perifoveal temporal retinal thickness; PEIT: Perifoveal inferior retinal thickness; PENT: Perifoveal nasal retinal thickness; C-T: Temporal choroidal thickness; C-F: Foveal choroidal thickness; C-N: Nasal choroidal thickness.

Table 5 Comparison of macular vessel density ratios of diabetic and idiophatic ERM cases and control group

MVR	d-ERM (*n*=50)	i-ERM (*n*=54)	Control (*n*=61)	*P*
MVRS	0.65±0.31	0.63±0.28	0.39±0.17	<0.001[b,c]
MVRD	0.76±0.18	0.82±0.26	0.70±0.17	0.007[c]

Conover-Iman or Bonferroni tests were performed for the binary comparisons among the groups and, the *P* value was set at 0.05. Significant differences were found between: b: dERM *vs* control; c: iERM *vs* control. d-ERM: Diabetic epiretinal membrane; i-ERM: Idiopathic epiretinal membrane; MVR: Macula vessel density ratio; MVRS: Macula superficial vessel density ratio; MVRD: Macula deep vessel density ratio.

central foveal thickness (CFT; r=0.528, P=0.000; r=0.527, P=0.000). A moderately positive correlation was detected between superficial VD of fovea and CFT in the diabetic ERM group (r=0.666, P=0.000). There was no relationship between deep VD of fovea and CFT in the diabetic ERM group.

In the control group, there was a weak correlation between superficial VD and retinal thickness, and a highly positive correlation between both superficial and deep foveal VD and CFT (r=0.294, P=0.021; r=0.838, P=0.000; r=0.689, P=0.000).

DISCUSSION

In this study, the retinal and choroidal vascular structures of idiopathic and diabetic ERM patients and a control group were compared with the help of OCT-A, and the effect of diabetes mellitus and ERM on vascular structures and the relationship between vascular structures and anatomical structures were evaluated.

FAZ can be determined quantitatively with the help of OCT-A, is a parameter that is affected by retinal microvascular changes and is an indicator of capillary drop-out. Macular foveal capillary structure was examined in common retinopathies with the help of OCT-A and suggested that ERM and its tangential forces disrupt the physiological macular structure and cause vascular displacement towards FAZ[10]. In our study, the FAZ area width was significantly smaller in ERM groups compared to the control group. It has been shown in previous studies that in eyes with ERM there is narrowing in the FAZ area due to tangential forces, and our results support the literature[11-12]. Although there was no significant difference in FAZ area between the diabetic and idiopathic ERM groups in our results, the FAZ width values were found to be lower in the iERM group. This can be explained by the expected FAZ enlargement due to capillary drop-out in diabetic retinopathy[7]. Similar to our results, in a prior study revealed that eyes with ERM exhibited notably higher foveal VD compared to the control group, and this was the result of central displacement of the foveal capillaries[8]. In the comparison of macula deep VD in our study, there was no significant difference between the three groups in terms of foveal deep VD values. However, the macula deep VD values of the ERM groups were found to be significantly lower than the control group in all quadrants, except the fovea. This suggests that the influence of ERM is primarily observed in the inner retinal layers and superficial vascular structures, yet it also highlights its impact on the deeper vascular structures due to ERM traction[12]. In the literature, there are cases in which visual abnormalities may be present without any deterioration in the ellipsoid zone or decrease in visual acuity, and this may be related to the effect of the ERM on the inner retinal layers[13]. In a study conducted with OCT-A, it was shown that there were significant changes especially in the SCP in eyes with ERM; the FAZ area created by SCP was smaller in eyes with ERM than in the macular pseudohole and control groups, and it was suggested that ERM caused a decrease in VD with a direct effect on SCP. The linear and continuous ERM structure creates a stronger mechanical effect on the superficial retinal vessels, impacting them first, and the DCP may be preserved[14].

There are also examples suggesting that narrowing of in the FAZ area may be the result of stretching and displacement of both SCP and DCP structures in ERM patients[15-16]. Optical coherence tomography-mediated studies have supported this idea and shown that the ellipsoid zone and photoreceptor layer are impaired in eyes with ERM[17-18]. In one study, a negative correlation between FAZ area and CFT was demonstrated in individuals with ERM. Interestingly, CFT decreased after vitrectomy, but no change was found in the FAZ area. These results suggest that ERM affects the outer retina more than the inner retina. In the same study, postoperative BCVA was not significantly correlated with FAZ area; however, it was significantly correlated with CFT, suggesting that outer retinal changes may affect BCVA more than changes to the inner retina[19]. According to our results, deep VD in all quadrants, except the fovea, was lower in ERM groups. This supports the point that ERM may affect both SCP and DCP, and by extension, both the inner and outer retinal layers. The fact that there was no significant difference in foveal deep VD may be related to the later involvement of deep layers. The mechanical stress associated with the ERM directly affects the inner retinal layer, so it is plausible that the vessels of the SCP are primarily affected by the ERM and may subsequently cause proportional deterioration in the DCP[12].

In our study, a moderate correlation was observed between superficial and deep foveal VD and CFT in the iERM group, and a high degree correlation was found in the control group. In the diabetic group, a similar relationship could not be demonstrated between the deep plexus and CFT. This positive relationship between foveal VD and CFT may reflect the increased metabolic demand resulting from increased retinal thickness in the control group.

In another study, it was found that the size of the FAZ was inversely proportional to the CFT, which was thought to be associated with the vascular response to increased metabolic demand in the thickened retina[20]. Examples in the literature suggest that there is a decrease in parafoveal VD in eyes with ERM, and this may be an indicator of neuronal damage secondary to mechanical distortion due to ERM. Given the belief that vascular insufficiency in eyes with ERM arises as a consequence of mechanical retinal distortion, the increase of CFT could potentially lead to a reduction in both the FAZ area and the VD in the parafoveal region. This phenomenon is

attributed to the deformation of the macular vascular structure due to tractional forces induced by ERM[12]. The positive correlation observed in our study between CFT and vessel densities could be linked to ERM-associated mechanical distortion. This distortion might manifest as an angiographic reflection of vascular changes even before significant vascular insufficiency becomes apparent.

Although there was no statistically significant difference between the ERM groups in terms of macula superficial VD values, all values were lower in the diabetic group. When macula deep VD values were compared, no significant loss of VD was observed in the diabetic group; however, this was not the case with macula superficial VD comparisons. This may suggest that the effect of diabetes is more pronounced in the superficial layers. In contrast to our study results, another research using OCT-A did not observe any changes in SCP before and after surgery in idiopathic and diabetic ERM cases; however, they did find that diabetic ERM cases showed an enlargement in the FAZ area within the DCP after surgery[21].

According to our results, choriocapillaris flow area was significantly lower in the diabetic ERM group compared to the other groups. There was no difference between the iERM and control groups, and the lack of difference suggests that the choriocapillaris flow area may have been affected by diabetes mellitus with a high probability[22]. There are studies reporting that changes related to FAZ are more common in the DCP than the SCP in diabetic retinopathy. However, these studies cannot explain the preservation of the SCP in diabetic retinopathy despite direct exposure to mechanical stress[23-24]. In our study results, the higher loss of superficial VD values in the diabetic group, as compared to the idiopathic group, may be related to the direct effect of the abnormal traction forces on the SCP created by diabetes. On the other hand, the fact that the loss of choriocapillaris flow area is higher in the diabetic group supports the aforementioned effect of diabetes on the DCP.

Lee *et al*[25] showed that decreased disc-foveal distance and vascular arcadeal distance, which are indicators of macular contraction, are associated with early visual loss in ERM progression. This demonstrates the importance of tangential forces in influencing early vision loss in idiopathic ERM. As the tangential forces exerted by the ERM cause a vascular shift, OCT-A seems promising as a tool to visualize this phenomenon, especially since depth selectivity can provide more information on the effect of tractional forces on deeper retinal layers. The aforementioned vascular shift led to the concept of MVR quantifying the extent of vascular shift in different layers. We found a significant increase in the superficial MVR in ERM patients in comparison to healthy controls, which presumably reflects a vascular displacement from the parafoveal to the foveal area. Another study found higher full-thickness and deep macular VD ratios in the ERM group, indicating ERM-related retinal distortion's influence on blood vessel distrubiton and density in the macula[8]. It is noteworthy that the deep MVR did not differ significantly in the diabetic group, which may be related to the fact that diabetic vascular damage is more prominent in the DCP and creates FAZ enlargement, especially in the deep layers[23-24]. Therefore, ERM-related tractional vascular displacement may not have an effect on the DCP in diabetic individuals as it does in the idiopathic group.

Although OCT-A is a new and non-invasive imaging technique that provides detailed visualization of the foveal capillary structure without dye injection, it has some limitations in terms of ERM imaging. One of them is image artifacts. The ERM itself may be producing image artifacts that could distort the assessment of vascular slippage. Another important issue is the segmentation problem. If the foveal structure is markedly impaired by ERM, automated software segmentation may not be sensitive enough to consistently recognize the correct retinal layers, leading to inaccurate thickness measurements.

In summary, our study has revealed significant anatomical and vascular changes in ERM cases compared to the control group. By utilizing OCT-A imaging, we identified distinct changes in diabetic and idiopathic ERM cases. The diabetic group showed lower superficial VD in all quadrants, indicating a pronounced effect of diabetes on the superficial layers. The iERM group exhibited the lowest FAZ area, due to expected FAZ enlargement in diabetic retinopathy. Moreover, choriocapillaris flow area was significantly lower in the diabetic ERM group. These findings emphasize the contrubiton of both mechanical distortion from ERM and diabetes-related microvasculopathy in diabetic ERMs. Our findings provide valuable insights into the pathophysiology of ERM, improving our understanding of the underlying mechanisms involved. Accurate determination of the cause of increased retinal thickness in the ERM cases is essential for diagnosis, treatment selection, and prognosis prediction. OCT-A plays a crucial role in distinguishing ERM-induced tangential forces and macular edema resulting from inner blood-retinal barrier dysfunction. It aids in differentiating these conditions and assessing the relationship between retinal thickness and vascular integrity.

The present study is significant as it utilizes OCT-A to conduct a non-invasive, comprehensive evaluation of vascular and anatomical retinochoroidal changes in patients with idiopathic and diabetic ERMs. However, further comprehensive and longitudinal investigations are needed to differentiate ERM-induced vasculopathy from diabetes-induced vasculopathy in diabetic ERM cases and gain a deeper understanding of their individual effects.

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