Research Article / Araştırma Makalesi

Evaluation of Neurodegenerative and Microvascular Changes in Branch Retinal Vein Occlusion After Regression of the Macular Edema

Retinal Ven Dal Tıkanıklığında Makula Ödeminin Gerilemesi Sonrası Mikrovasküler ve Nörodejeneratif Değişikliklerin İncelenmesi

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Abstract

Background: To evaluate the quadrantal effect of branch retinal vein occlusion (BRVO) on retinal microvasculature and ganglion cell-internal plexiform layer thickness (GC-IPL)
Materials and Methods: This retrospective study included 62 eyes of 31 patients diagnosed with unilateral BRVO. Participants had optical coherence tomography (OCT) and OCT angiography (OCTA) analyses after complete regression of the macular edema. The macular central subfield thickness (CST), GC-IPL thickness, vessel and perfusion density (VD and PD), and foveal avascular zone (FAZ) area of the superficial capillary plexus (SCP) were evaluated in both groups. We also compared the affected and opposite unaffected quadrant measurements in BRVO eyes with the corresponding quadrant to BRVO (BRVO-corresponding) in the fellow eye.
Results: The mean FAZ area, VD, and PD of SCP demonstrated no significant difference between BRVO and fellow eyes of BRVO ($p>0.05$ all). The mean GC-IPL thickness, the mean VD of the parafoveal and perifoveal ring, and mean PD of the perifoveal ring were significantly decreased in the affected quadrant of BRVO eyes ($p<0.05$ all). In the post hoc tests, the VD of the parafoveal and perifoveal ring was significantly lower in the affected quadrant than the unaffected and BRVO-corresponding quadrant ($p<0.05$ all). A post hoc analysis revealed that the PD was significantly lower in the affected quadrant than the unaffected and BRVO-corresponding quadrant ($p=0.017$, $p=0.025$).
Conclusions: The microvascular changes in the macular superficial capillary plexus accompany significant ganglion cell loss in BRVO. The microvascular and microstructural alterations were mainly localized to the distribution area of the occluded vein.

Key Words: Retinal blood vessels, Retinal vein occlusion, Macular edema

Öz.

Amaç: Retinal ven dal tıkanıklığının (RVDT) makuler mikrovasküler yapı ve ganglion hücre-iç pleksiform tabaka (GC-IPL) kalınlığı üzerindeki sektöryel etkilerini araştırmak.
Materyal ve Metod: Bu retrospektif çalışmaya, RVDT tanılı 31 olgunun hastalıktan etkilenen ve sağlıklı gözleri olmak üzere 62 göz dahil edildi. Olguların makula ödeminin gerilemesini takiben optik koherens tomografi (OKT) ve optik koherens tomografi anjiyografi (OKTA) ile görüntülemeleri yapıldı. İki grupta, santral makuler kalınlık, GC-IPL kalınlığı, yüzeyel kapiller pleksusun (SCP) damar yoğunluğu (VD), perfüzyon yoğunluğu (PD) ve foveal avasküler zon (FAZ) alanı analizi yapıldı. RVDT'li gözlerde etkilenen sektör ve etkilenmeyen sektörün ölçümleri hesaplanarak, sağlıklı gözlerde RVDT ile yöndeş (RVDT-yöndeş) olan sektöre ait ölçümlerle karşılaştırıldı.
Bulgular: RVDT'li gözler ve sağlıklı diğer gözleri arasında ortalama FAZ alanı açısından istatisitksel olarak anlamlı fark bulunmadı. SCP'nin VD ve PD ölçümleri açısından olguların RVDT'li ve diğer gözleri arasında istatistiksel olarak anlamlı fark bulunmadı. Ortalama GC-IPL kalınlığı, iç ve dış halka VD ve dış halka PD değerleri RVDT'li gözlerde istatistiksel olarak anlamlı düşüktü ($p<0,05$). Post-hoc analizlerde, iç ve dış halka VD ölçümleri etkilenen sektörde, etkilenmeyen sektör ve RVDT ile yöndeş sektöre göre istatistiksel olarak anlamlı düşüktü ($p<0,05$). Post-hoc analizine göre PD ölçümleri etkilenen sektörde, etkilenmeyen ve RVDT ile yöndeş sektöre göre istatisitksel olarak anlamlı düşük saptandı ($p<0.05$).
Sonuç: Maküler yüzeyel pleksustaki mikrovasküler değişiklikler, BRVO'da anlamlı ganglion hücre kaybına eşlik eder. Mikrovasküler ve mikroyapısal değişiklikler esas olarak tıkanmış damarın dağılım alanına lokalizedir.

Anahtar kelimeler: Retina damarları, Retinal ven tıkanıklığı, Maküla ödemi

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Introduction

Branch retinal vein occlusion (BRVO) is a common retinal vascular disease that has significant impacts on visual acuity. Previous studies have revealed that about 13.9 million adults are affected by BRVO worldwide (1). The disease may be either asymptomatic or symptomatic due to the site and severity of the occlusion. The prognosis of BRVO depends on the coexistence of macular edema and ischemia, neovascularization, and vitreous hemorrhage (2). Venous occlusion results in hypoxia and increased vascular endothelial growth factor (VEGF) levels. Consequently, vessels become more permeable, and macular edema (ME) develops in BRVO (3). Intravitreal anti-VEGF injections are the standard treatment modality for BRVO associated ME. However, anatomic response and visual impairment are not correlated in many patients having anti-VEGF therapy (4). Macular microstructural changes are thought to be the main cause of the discrepancy between the anatomical response and visual acuity gains. Hypoxia triggers an apoptotic and necrotic process that results in retinal ganglion cell death and neural degeneration in BRVO (5). Optical coherence tomography (OCT) segmentation enables the assessment of retinal ganglion cells objectively. Previous OCT studies demonstrated thickness alterations in different retinal layers in BRVO patients (6-8).

Fluorescein angiography (FA) is the imaging modality in evaluating macular edema, non-perfusion areas, and new vessels in retinal vascular diseases. However, it is difficult to assess the foveal capillaries and avascular zone (FAZ) with FA due to the leakage and capillary superposition (9-10). OCTA is a novel tool that enables non-invasive evaluation of perifoveal capillaries and macular ischemia. The instruments also provides quantitative assessment of capillary plexuses (11).

In this study, we aimed to assess the alterations in retinal ganglion cells and macular microvasculature after regression of macular edema secondary to BRVO using OCT and OCTA.

Materials and Methods

Study participants

This retrospective cross-sectional study was conducted in accordance with the Declaration of Helsinki and approved by the Hamidiye Ethics Committee of the University of Health Sciences (16/06/2020-E.18347). All participants were recruited from Beyoglu Eye Training and Research Hospital and provided informed consent before the procedures. Consecutive 31 patients treated and followed up with unilateral BRVO associated ME, in the retina clinic between September 2019 to February 2020 were enrolled.

The inclusion criteria were the existence of regressed ME secondary to unilateral BRVO and a healthy fellow eye. At the time of enrollment, BRVO eyes were demonstrated complete regression of hyporeflective cystoid lesions, serous macular detachment, and retinal hemorrhages. Eyes with CRT <280 μm and morphologically normal foveal profile for at least three consequtive months were included. Exclusion criteria were as follows: axial length ≤22 mm and ≥ 26 mm, myopia greater than six diopters (D), patients with a history of stroke and myocardial infarction, neurological disorders, prior ocular surgery except with cataract surgery, ocular hypertension and glaucoma, intraocular inflammation, coexisting retinal or optic disc pathology, images with poor signal strength (SS) <7/10).

Ocular Examinations

All patients who were eligible had undergone a comprehensive ophthalmologic examination including best-corrected visual acuity (BCVA) assessment, intraocular pressure (IOP) measurement using an applanation tonometer, biomicroscopic examination, and fundoscopic examination. Cirrus 5000 HD OCT with AngioPlex OCT Angiography device was used by a one trained operator (SO) for both OCT and OCTA imaging.

Acquisition of OCT and OCTA images

The Macular Cube 512 × 128 scan protocol provides the central subfield thicknesses (CST) and average ganglion cell - parafoveal plexiform layer (GC-IPL) thickness measurements. GC-IPL thickness is automatically calculated for six quadrants according to the ETDRS grid. Macular microvasculature was evaluated using the 6x6 volume angiography scan protocol. In superficial capillary plexus (SCP), borders of the foveal avascular zone (FAZ) area were automatically delineated and corrected manually if deemed necessary. The FAZ area and vessel density, perfusion density (VD and PD) of the SCP were automatically provided based on the standard ETDRS subfields. The inner and outer ring in the overlay ETDRS grid corresponds to the parafoveal and perifoveal region, respectively. We also calculated and compared the GC-IPL, VD, and PD measurements of the affected quadrant and opposite unaffected quadrant in BRVO eyes with the corresponding quadrant to BRVO (BRVO-corresponding) in the fellow eye.

Statistical analysis

Statistical analyses were done using SPSS 25.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was performed to evaluate the conformity of the data to a normal distribution. The continuous variables were compared using the Independent samples t-test. The mean OCT and OCTA parameters in affected, unaffected, and corresponding quadrants were compared using the one-factor ANOVA. The differences among groups were evaluated using the Bonferroni post- hoc test. A p-value <0.05 was considered statistically significant.

Results

Patient characteristics

In this study, a total of 62 affected and unaffected fellow eyes of 31 patients with unilateral BRVO were included. There were 14 (45%) male and 17 (55%) female patients, and the mean age was 60.71±11.56 years. The mean BCVA was 0.63±0.39 logMAR at presentation. The mean BCVA was improved to 0.49±0.42 logMAR at the time of OCTA imaging. The mean time between the BRVO diagnosis and OCTA imaging was 19.74±23.43 months. Demographics and clinical information of the patients are presented in Table 1.

Table 1. Demographics and clinical characteristics of the BRVO patients

Age, mean±SD, years	60.71±11.56
Gender (n, male/female)	14/17
Laterality (right/left)	15/16
BRVO location, n (%)	
Superior	26 (84.9%)
Inferior	5 (16.1%)
Previous treatment history, n (%)	
Anti-VEGF	27 (87.1%)
Dexamethasone implant	10 (32.2%)
Laser photocoagulation	10 (32.2%)
BCVA mean±SD, logMAR	
Baseline	0.63±0.39
At the time of OCTA imaging	0.49±0.42
Duration of follow-up, mean±SD, months	19.74±23.43
Systemic diseases, n (%)	
Hypertension	14 (45.1%)
Diabetes	8 (25.8%)

BCVA: Best corrected visual acuity,
OCTA: optical coherence tomography angiography.

Analysis of OCT and OCTA measurements

The mean CST was 254.71±23.54 μm and 254.24±22.80 μm in the BRVO and fellow eyes, respectively. The mean GC-IPL of BRVO eyes was slightly thinner compared to the fellow eyes of BRVO. However, the difference was not statistically significant (p=0.841). The mean FAZ area also showed no significant difference between the BRVO and fellow eyes (p=0.385). In OCTA imaging, the mean VD and PD parameters showed no significant difference between the BRVO and fellow eyes (Table 2).

GC-IPL and OCTA measurements were also compared in affected and unaffected quadrants of BRVO eyes, with the BRVO-corresponding quadrant in the unaffected fellow eyes (Figure 1). Table 3 provides detailed information about quadrant based comparisons among groups and post hoc analysis tests. The mean GC-IPL thickness was 70.57±23.28, 74.96±17.09, and 83.41±8.52 in the affected, unaffected, and BRVO-corresponding quadrant, respectively (p=0.015). In the post hoc analysis, the GC-IPL thickness of the affected quadrant was significantly thinner than the BRVO-corresponding quadrant of the fellow eye (p=0.014).

Table 2. Quantitative OCT and OCTA analysis in the BRVO and fellow eyes

	BRVO eyes	Fellow eyes	p^*
CST (μm)	254.71±23.54	254.24±22.80	0.935
GC-IPL (μm)	73.93±22.27	75.07±19.43	0.841
FAZ area (mm^2)	0.28±0.19	0.24±0.13	0.385
Vessel density (mm^{-1})			
Central	8.54±4.70	8.52±4.11	0.983
Parafoveal ring	15.37±4.21	16.9±3.86	0.170
Perifoveal ring	15.47±2.68	16.66±2.57	0.103
Full area	15.42±2.86	16.78±2.90	0.089
Perfusion density (%)			
Central	18.56±9.37	18.74±10.91	0.950
Parafoveal ring	35.18±9.25	38.21±7.40	0.190
Perifoveal ring	40.43±6.12	42.20±6.53	0.307
Full area	37.80±7.07	40.21±6.64	0.204

CST: Central subfield thickness, FAZ: Foveal avascular zone,
GC-IPL: Ganglion cell-parafoveal plexiform layer.
Values are means±standard deviation for all subjects in each group.
**Independent samples t test p<0.05 was set as statistically significant.*

Among quadrant based subgroups, a significant difference was observed in SCP parafoveal and perifoveal VD measurements (p=0.009, p= 0.001, respectively). The mean parafoveal and perifoveal VD were significantly decreased in the BRVO affected quadrant compared to the unaffected and BRVO-corresponding quadrant (p<0.05 all). The PD measurements of the perifoveal ring demonstrated a significant difference among three groups, in contrast to parafoveal ring PD measurements (p=0.008, p=0.056, respectively). A post hoc analysis revealed the mean PD of the affected quadrant was significantly decreased compared to the unaffected and BRVO-corresponding quadrant (p= 0.017, p= 0.025, respectively).

Discussion

In this study, we demonstrated that BRVO eyes had significantly thinner GC-IPL and decreased VD and PD in the affected region of BRVO eyes. These findings support vascular mediated neuronal damage and neurodegenerative process in BRVO patients.

Retinal hypoxia causes photoreceptor cell damage and irreversible neuronal degeneration that results in permanent visual loss in BRVO. The innermost retina, particularly the retinal ganglion cells (RGCs), are more vulnerable to acute hypoxia (12).

Table 3. Comparison of GC-IPL and OCTA parameters between quadrant based subgroups in BRVO and fellow eyes

	BRVO eyes		Fellow eyes	p^{*}	$p^{¶}$		
	Affected quadrant (a)	*Unaffected quadrant (b)*	*BRVO-Corresponding quadrant (c)*	*(a,b,c)*	*a-b*	*a-c*	*b-c*
GC-IPL thickness (μm)	70.57±23.28	74.96±17.09	83.41±8.52	0.015	0.970	0.014	0.176
Vessel density (mm^{-1})							
Parafoveal ring	14.32±3.91	16.65±4.07	17.08±3.07	0.009	0.046	0.013	0.998
Perifoveal ring	15.87±3.06	18.09±2.43	18.27±2.42	0.001	0.004	0.002	0.998
Perfusion density (%)							
Parafoveal ring	33.00±9.05	36.83±9.86	38.06±6.28	0.056	0.242	0.065	0.998
Perifoveal ring	38.22±6.88	42.47±5.27	42.29±5.49	0.008	0.017	0.025	0.999

Values are means±standard deviation for all subjects in each group.
**One factor ANOVA test*
¶Bonferroni post hoc test
p<0.05 was set as statistically significant.

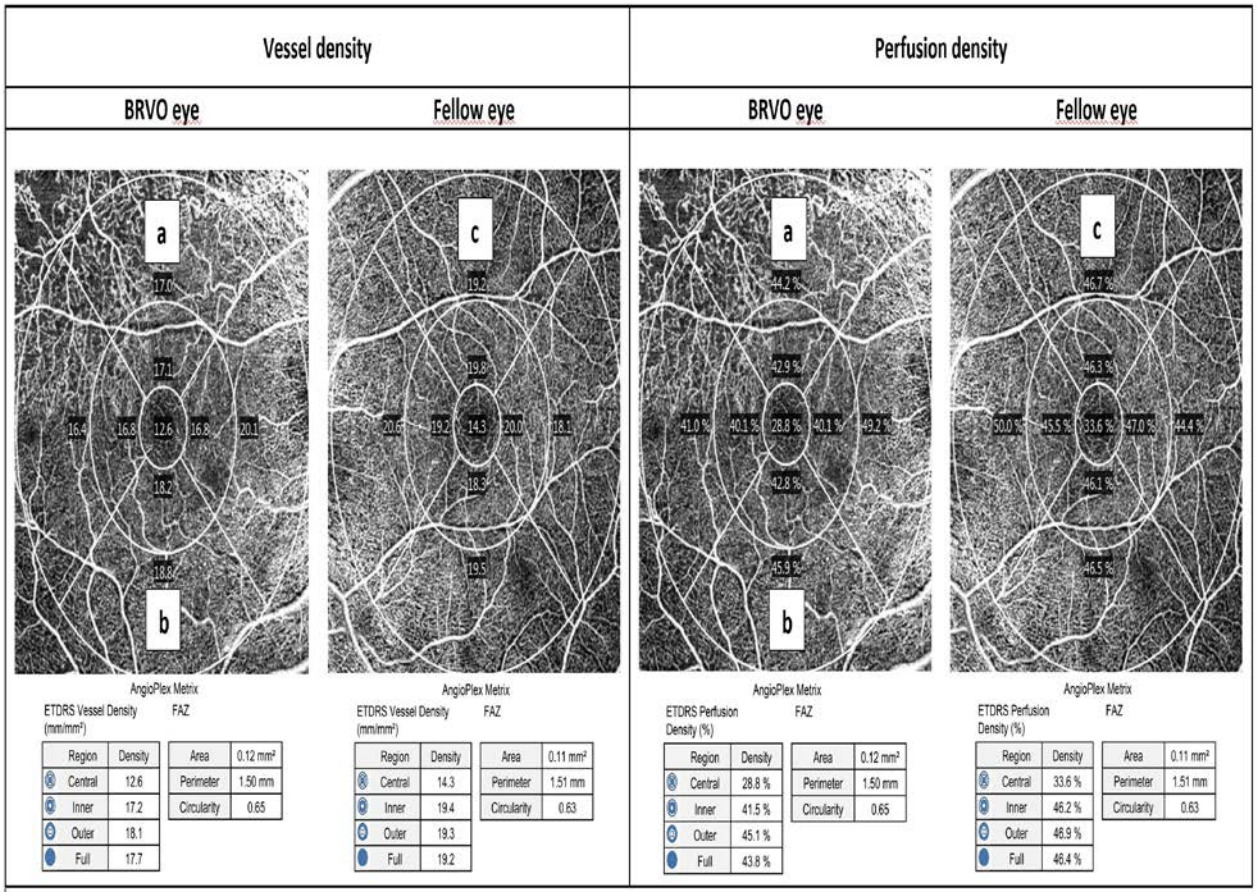

Figure 1. OCTA imaging of a patient with superior BRVO in the right eye. Vessel density and perfusion density of the superficial capillary plexus is decreased in the affected quadrant (a) compared to the opposite unaffected quadrant (b) and BRVO- corresponding quadrant (c) in the fellow eye (first row). Quantitative assessment of vessel density and perfusion density in BRVO and fellow eyes (second row).

Lee et al. showed that in BRVO patients ME may cause low repeatable GC-IPL thickness measurements using OCT (13). In this study, we evaluated the GC-IPL after regression of ME and observed thinner GC-IPL in BRVO eyes than their fellow eyes. However, this difference was not statistically significant. Kim et al. evaluated the alterations in GC-IPL thickness in non-ischemic CRVO after regression of ME and found that GC-IPL was significantly thinner in the ME group than CRVO without ME (8). In quadrant based analysis, we found a significant difference in GC-IPL thickness between the affected quadrant and BRVO-corresponding quadrant of the fellow eye. Similarly, Lim et al. demonstrated significant RNFL and GC-IPL thinning in the retinal area that affected from BRVO compared to the corresponding retinal area in the fellow eyes (14).

In this study, the overall mean VD and PD of superficial

plexus were reduced in BRVO eyes compared to their unaffected eyes. However, the difference was not statistically significant. Kouslis et al. demonstrated that the VD of the SCP in BRVO eyes was significantly decreased compared to their fellow eyes (11). On the other hand, Mastropasqua et al. demonstrated the overall parafoveal VD was significantly lower in the BRVO eyes than controls (15). The discrepancies between studies may be related to differences in study designs, scan protocols, and OCTA platforms used in the studies.

Another OCTA parameter, the mean FAZ area, showed no significant difference between BRVO and fellow eyes. Suzuki et al. reported FAZ enlargement after anti-VEGF therapy in superficial and deep plexuses in eyes with retinal vein occlusion (16). Adhi et al. revealed that the FAZ area was the greatest in RVO eyes, and larger in the unaffected eyes of RVO patients than controls (17). We should interpret these conflicting results, considering that the FAZ measurements also may vary in healthy subjects (18,19).

In contrast to overall VD and PD analyses, we found significant differences in VD of the parafoveal and perifoveal ring and PD of perifoveal ring among affected, unaffected, and corresponding quadrants. In accordance with our study, Samara et al. found a significant decrease in the mean VD of the affected sectors of BRVO eyes compared to unaffected eyes (20). In a study investigating the parafoveal perfusion status of retinal capillary plexuses in eyes with resolved BRVO, Manabe et al. showed 85.2% of the patients had capillary non-perfusion in the SCP in the BRVO affected region (21). In a recent study, Brar et al. evaluated the OCTA parameters in the affected and unaffected quadrant in BRVO (22). They found that VD and PD of the parafoveal and perifoveal ring significantly reduced in the affected quadrant.

In contrast to Brar et al., we also included the BRVO -corresponding quadrant in the fellow eye for quadrantal subgroup analysis. The post hoc analysis of groups revealed that the affected quadrant showed significant retinal microvascular changes compared to both unaffected and BRVO-corresponding quadrants. These findings support that significant capillary ischemia and hypoxia may lead to permanent damage to the retinal ganglion cells in BRVO.

Our study had several limitations. Owing to retrospective design of this study, patients were evaluated at different stages of BRVO. The natural course of the disease and different treatment regimens, such as laser and intravitreal injections, may affect the parameters that we investigated, including GC-IPL, VD, and PD. In addition, we evaluated the OCTA parameters based on superior and inferior sectors in quadrant based analyses. However, this topographic distribution does not fully cover the area affected by BRVO. Although accurate segmentation may not be possible in the presence of ME, the lack of data on baseline OCTA and FA for retinal ischemia is another limiting factor. Further prospective studies evaluating the association between neurodegeneration and macular microvasculature using broad scan areas are needed to clarify the neurodegenerative process in BRVO.

In conclusion, this study demonstrates that microvascular changes in the macular SCP accompany significant ganglion cell loss in BRVO. The microvascular and microstructural alterations were mainly localized to the affected region where corresponds to the distribution area of the occluded vein.

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Ethical approval: Ethical approval was obtained from Hamidiye Ethics Commitee of University of Health Sciences for this study (16/06/2020-E.18347).

Authorship Contributions: Design, conduction and review of the study (SO), data collection, and statistical analysis (YO).

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