Original Article

Quantification of retinal microvasculature and neurodegeneration changes in branch retinal vein occlusion after resolution of cystoid macular edema on optical coherence tomography angiography

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Purpose: To compare foveal avascular zone (FAZ) area and circularity, ganglion cell layer (GCL) thickness, retinal perfusion density (PD), and vessel density (VD) in eyes with branch retinal vein occlusion (BRVO) after resolution of cystoid macular edema (CME) to fellow control eyes and to correlate these parameters with visual acuity (VA). **Methods:** SD-OCTA scans (Zeiss Angioplex; Carl Zeiss Meditec Version 10) obtained on 32 eyes with BRVO after resolution of the CME with their fellow eyes used as controls were retrospectively evaluated. Parameters analyzed were FAZ size and circularity, PD, and VD in the superficial capillary plexus measured in the Early Treatment Diabetic Retinopathy Study (ETDRS) grid pattern using the automated algorithm. GCL thickness was generated from the Macular Cube 512 × 218 protocol. VA measured on the same day as OCTA examination was recorded. **Results:** The mean FAZ area was greater (P = 0.01) in BRVO eyes (0.239 ± 0.108 mm^2) when compared with fellow eyes (0.290 ± 0.127 mm^2). The FAZ was more irregular in BRVO eyes compared with fellow eyes (circularity index = 64.6 ± 12.8% vs 71.1 ± 10.8%, respectively, P = 0.03). GCL thickness was lower in BRVO eyes compared with control eyes (67.19 ± 27.71 vs 77.79 ± 6.41 respectively, P = 0.006). The mean VD and PD were significantly lower in the ETDRS outer ring in BRVO eyes (P = 0.04 and 0.038, respectively). On comparison of the affected quadrant with the unaffected quadrant in BRVO eyes, the affected quadrant had a lower outer PD (P = 0.04), outer VD (P = 0.04), and GCL thickness (P = 0.02). There was no significant correlation of VA with FAZ, VD, or GCL thickness (P > 0.05). **Conclusion:** FAZ is more irregular and enlarged, and GCL is thinner, in eyes with BRVO after resolution of CME especially in the affected quadrant suggesting neuronal degeneration as a sequela of BRVO. Both perfusion and VD are reduced in the quadrant affected by the BRVO demonstrating regional quantitative differences in the retinal microvasculature. These parameters may prove useful in monitoring the disease progression and treatment response.

Key words: Branch retinal vein occlusion, foveal avascular zone, macular edema, optical coherence tomography, optical coherence tomography angiography

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_1554_18

Quick Response Code:

Cystoid macular edema (CME) is a predominant cause of vision loss in branch retinal vein occlusion (BRVO).[1] Laser, antivascular endothelial growth factor injections, and intravitreal steroids have been reported to be effective in reducing macular edema and improving vision.[2-7] However, poor visual recovery has been reported despite complete resolution of macular edema.[2,8] Thus, there is an urgent need to improve our understanding of pathophysiologic mechanism and anatomic correlates for visual loss due to these disorders.

Fundus fluorescein angiography (FFA) has been used in the past to visualize retinal circulation and helped us to understand pathogenic mechanisms leading to visual loss in such diseases.[9,10] But with the advent of optical coherence tomography angiography (OCTA), this process has become much rapid and noninvasive.[11-16] To date, several studies using OCTA have reported about vascular changes in BRVO,[17-19] and possible association between retinal vessel density (VD) and VA has also been reported.[20]

Furthermore, experimental studies have also shown that retinal ganglion cells (RGCs) are damaged in BRVO suggesting that BRVO also has a significant neuronal component underlying its pathogenesis along with microvascular changes.[21]

In this study, we collectively evaluated all these OCTA parameters, area and circularity of the foveal avascular zone (FAZ), quantitative areas of vascular perfusion, and ganglion cell damage after treatment of CME in BRVO, and assessed their relationship with each other and the visual outcome.

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Received: 14-Sep-2018 Revision: 03-May-2019
Accepted: 21-Jun-2019 Published: 22-Oct-2019

Cite this article as: Brar M, Sharma M, Grewal SP, Grewal DS. Quantification of retinal microvasculature and neurodegeneration changes in branch retinal vein occlusion after resolution of cystoid macular edema on optical coherence tomography angiography. Indian J Ophthalmol 2019;67:1864-9.

Methods

The procedures used in this study conformed to the tenets of the Declaration of Helsinki and were approved by the Institutional Review Board. All patients were informed of the nature and possible consequences of the procedures, and signed informed consent was obtained from all patients. A consecutive series of patients who showed complete resolution of center-involved macular edema associated with BRVO and underwent OCTA and spectral domain optical coherence tomography (SD-OCT) examination at the Department of Retina at Grewal Eye Institute, Chandigarh, between September 2015 and April 2017 were enrolled in this retrospective observational study. All patients had a previous history of BRVO with retinal hemorrhage and macular edema extending to the fovea diagnosed by SD-OCT and FFA. The previous treatment included intravitreal ranibizumab, intravitreal bevacizumab, intravitreal Ozurdex implant, and laser photocoagulation; some patients had received a combination of two or more treatments for complete resolution of their macular edema.

Eyes with history of glaucoma and optic nerve disorder were excluded. Contralateral eyes were used as control eye if they had no pathology. All patients underwent comprehensive ophthalmic evaluation including measurement of best-corrected visual acuity (BCVA), binocular indirect ophthalmoscopy, contact lens, slit-lamp biomicroscopy, and fundus photography.

OCT and OCTA imaging

Images were acquired with Zeiss Cirrus Angioplex (Carl Zeiss Meditec, Dublin, CA, USA). A 6 × 6 mm area, centered on the fovea, was captured in all eyes. The Angioplex software (version 10.0) automatically segments the vascular area into four layers, that is, the superficial capillary plexus (SCP), deep capillary plexus, outer retina, and choroidal levels. Default autosegmentation of the SCP images includes the vasculature from the internal limiting membrane to 15 µm below the inner plexiform layer (IPL).

We also qualitatively assessed the disruption of the FAZ based on the previous report.[17-19] The disruption of the FAZ was defined as loss of the intact perifoveal capillary arcade greater than one quadrant. Image analyses were performed by two masked observers (MB and MS). When there was disagreement, a third investigator (DG) was consulted for the final decision.

We quantitatively evaluated the SCP using the Angio Analytics software (version 10), which measures the flow area and non-flow area of each layer. For quantitative analysis, the vascular area was measured as the area of visible perfusion and vascular density in the SCP within a 6 × 6-mm area. Eyes with preexisting macular disease, history of vitrectomy surgery, glaucoma, optic nerve disease, media opacity that could interfere with OCTA examinations, and imaging interpretation were excluded from data analysis. OCTA images with poor quality (a signal strength index 5) motion artifacts, or incorrect auto segmentation were also excluded from the data analysis.

OCT images were acquired before and after treatment of CME. Central retinal thickness (CRT) was measured automatically as the average retinal thickness in the central area. Eyes with CRT <280 µm and morphologically normal foveal profile were included in the study. One macular scan was acquired using the Macular Cube 512 × 128 scan protocol where 6 × 6 mm area centered on the fovea was scanned with 128 horizontal B-scans, each consisting of 512 A-scans per B-scan (total of 65,536 sampled points) within a scan time of 2.4 s in each eye.[14] The automated Ganglion Cell Analysis algorithm, incorporated in Cirrus HD-OCT software, was used to demarcate and measure thicknesses of GC-IPL. The measurements were obtained within an elliptical annulus centered on the fovea based on the three-dimensional data generated from the Macular Cube 512 × 128 scan protocol. The Ganglion Cell Analysis algorithm measured thicknesses of the ganglion cell layer (GCL)-IPL of eight areas for each scan, determined by Early Treatment Diabetic Retinopathy Study grid: nasal, superior, temporal, inferior, nasal superior, nasal inferior, temporal superior, and temporal inferior. Thicknesses were calculated as the distance between two segmented hyperreflective intraretinal layers; GC-IPL thickness, which is the distance between outer boundaries of the RNFL and the IPL.

Statistical analysis

Descriptive statistics was applied to the various characteristics of BRVO and fellow control eyes. Paired *t*-test was used to find the difference between means of OCTA parameters for the BRVO and fellow control eyes. Spearman's correlation test was used for statistical comparison of quantitative OCTA parameters, FAZ area, GCL thickness, and VD with VA in 32 eyes with BRVO. A 95% confidence interval and a 5% level of significance were used; therefore, results with *P* value less than or equal to 0.05 were considered significant.

Results

Data were collected on ophthalmic history, demographics, CRT post treatment, VA after complete resolution of CME, OCTA quantitative analysis, and Automated Ganglion cell analysis. Our study included 62 eyes of 31 patients (21 male and 10 female). In all, 32 eyes had BRVO, 28 normal fellow eyes served as controls, and 2 were excluded from the control group because of underlying retinal pathology.

The baseline characteristics of the 32 eyes with resolved CME are summarized in Table 1. The mean patient age was 62.2 (45–79) years. The initial mean logMAR BCVA was 0.47. Patients had undergone treatment of center-involved CME by intravitreal ranibizumab [3 (8.3%)], intravitreal bevacizumab [10 (27.8%)], Ozurdex [1 (2.8%)], laser photocoagulation [3 (8.3%)], or a combination of above [19 (52.8%)]. The mean time interval between initial presentation with BRVO and OCTA imaging was 17.9 months. At the time of OCTA, the mean logMAR VA improved to 0.29 with resolution of macular edema in all eyes. BRVO location was found to be superior in 22 eyes (69%) and inferior in 10 eyes (31%).

GCL thickness

GCL thickness was analyzed by quadrant for BRVO and control eyes. Among BRVO eyes, the affected quadrant [superotemporal (ST) or inferotemporal (IT)] had a significantly thinner GCL (63.43 ± 16.19 µm) compared to the corresponding opposite unaffected quadrant (71.65 ± 16.94, $P = 0.02$) [Table 2 and Fig. 1d]. In contrast, there was no difference among the ST and IT quadrants in control eye (76.50 ± 6.21 vs 78.25 ± 7.73, respectively, $P = 0.15$) [Table 2]. BRVO eyes

Table 1: Characteristics of patients with BRVO and control subjects

Characteristic	Controls (*n*=28)	BRVO (*n*=32)
Age in years, mean (range)	61.2 (45-79)	62.2 (45-79)
Gender		
Male	20 (71.4%)	21 (67.7%)
Female	8 (28.6%)	10 (32.3%)
Previous treatment		
Intravitreal ranibizumab		3 (8.3%)
Intravitreal bevacizumab		10 (27.8%)
Ozurdex		1 (2.8%)
Laser photocoagulation		3 (8.3%)
Combination		19 (52.8%)
BCVA (logMAR mean)		
At presentation	-	0.47
BCVA at resolution of macular edema	-	0.29
Duration of follow-up		17.9 months
BRVO location		Superior - 22 (69%), inferior - 10 (31%)

BRVO=Branch retinal venous occlusion; BCVA=Best-corrected visual acuity, logMAR=Logarithm of minimal angle of resolution

Table 2: Comparison of GCL thickness among affected and unaffected quadrants in BRVO eyes and among opposite quadrants in control eyes

	GCL thickness in affected quadrant (μm: mean±SD)	GCL thickness in unaffected quadrant (μm: mean±SD)	*P*
Superior BRVO (*n*=22)	64.95±15.67	74.05±17.67	0.04
Inferior BRVO (*n*=10)	59.89±17.78	65.78±14.20	0.22
All BRVO eyes (*n*=32)	63.43±16.19	71.65±16.94	0.02
Control eyes	76.50±6.21 (superior)	78.25±7.73 (inferior)	0.15

GCL=Ganglion cell layer; BRVO=Branch retinal vein occlusion; SD=Standard deviation

Table 3: FAZ area and circularity, GCL thickness, VD, and PD in BRVO eyes compared with fellow control eyes

Group	FAZ		Ganglion cell layer average (μm)	VD		PD	
	Area (mm^2)	Circularity %		Inner ring	Outer ring	Inner ring	Outer ring
BRVO	0.239±0.108	64.6±12.8	67.19±27.71	16.03±2.57	15.64±1.86	38.5±7.3	38.8±4.4
Fellow control eyes	0.290±0.127	71.1±10.8	77.79±6.41	16.37±3.40	16.99±2.49	39.53±8.38	42.19±6.56
*P**	0.01	0.03	0.006	0.36	0.04	0.35	0.038

FAZ=Foveal avascular zone; GCL=Ganglion cell layer; VD=Vessel density; PD=Perfusion density; BRVO=Branch retinal vein occlusion; *Paired *t*-test for pairwise comparisons

demonstrated lower average GCL thickness compared with control eyes (67.19 ± 27.71 vs 77.79 ± 6.41, $P = 0.006$) [Table 3].

OCTA metrics

FAZ area disruption was present in all but one BRVO eye [Fig. 1g]. The mean FAZ area was greater ($P = 0.01$) in BRVO eyes (0.239 ± 0.108 mm^2) when compared with fellow eyes (0.290 ± 0.127 mm^2). The FAZ was more irregular in BRVO eyes compared with fellow eyes (circularity index = 64.6 ± 12.8% vs 71.1 ± 10.8%, respectively, $P = 0.03$) [Table 3 and Fig. 1e]. Among BRVO and control eyes, the mean inner ring perfusion density (PD) (38.5 ± 7.3% vs 39.53 ± 8.38%, respectively, $P = 0.35$) and inner ring VD (16.03 ± 2.57% vs 16.37 ± 3.40%, respectively, $P = 0.36$) were similar. However, BRVO eyes had a significantly reduced outer ring PD (38.8 ± 4.4% vs 42.19 ± 6.56%, respectively, $P = 0.038$) and outer ring VD (15.64 ± 1.86 vs 16.99 ± 2.49, respectively, $P = 0.04$) compared with controls [Fig. 1e, f and Table 3].

When a quadrant-based analysis was performed in BRVO eyes, the PD in the affected inner quadrant was significantly lower than the PD in the unaffected quadrant (37.93 ± 5.86% vs 42.29 ± 5.92%, respectively, $P = 0.01$), and a similar trend was seen for the outer affected and unaffected quadrants (36.05 ± 10.56% vs 41.20 ± 8.43, $P = 0.04$). The VD in the affected inner quadrant in BRVO eyes was lower than the VD in the unaffected quadrant (15.44 ± 2.72 vs 16.91 ± 3.14, $P = 0.06$) and was significantly lower in the affected outer quadrant compared with the unaffected outer quadrant (13.40 ± 3.86 vs 15.54 ± 3.47, respectively, $P = 0.04$).

The mean 6 × 6 mm PD was 39.8 ± 4.2% in BRVO eyes compared with 40.95 ± 6.88% in control eyes ($P = 0.28$). The

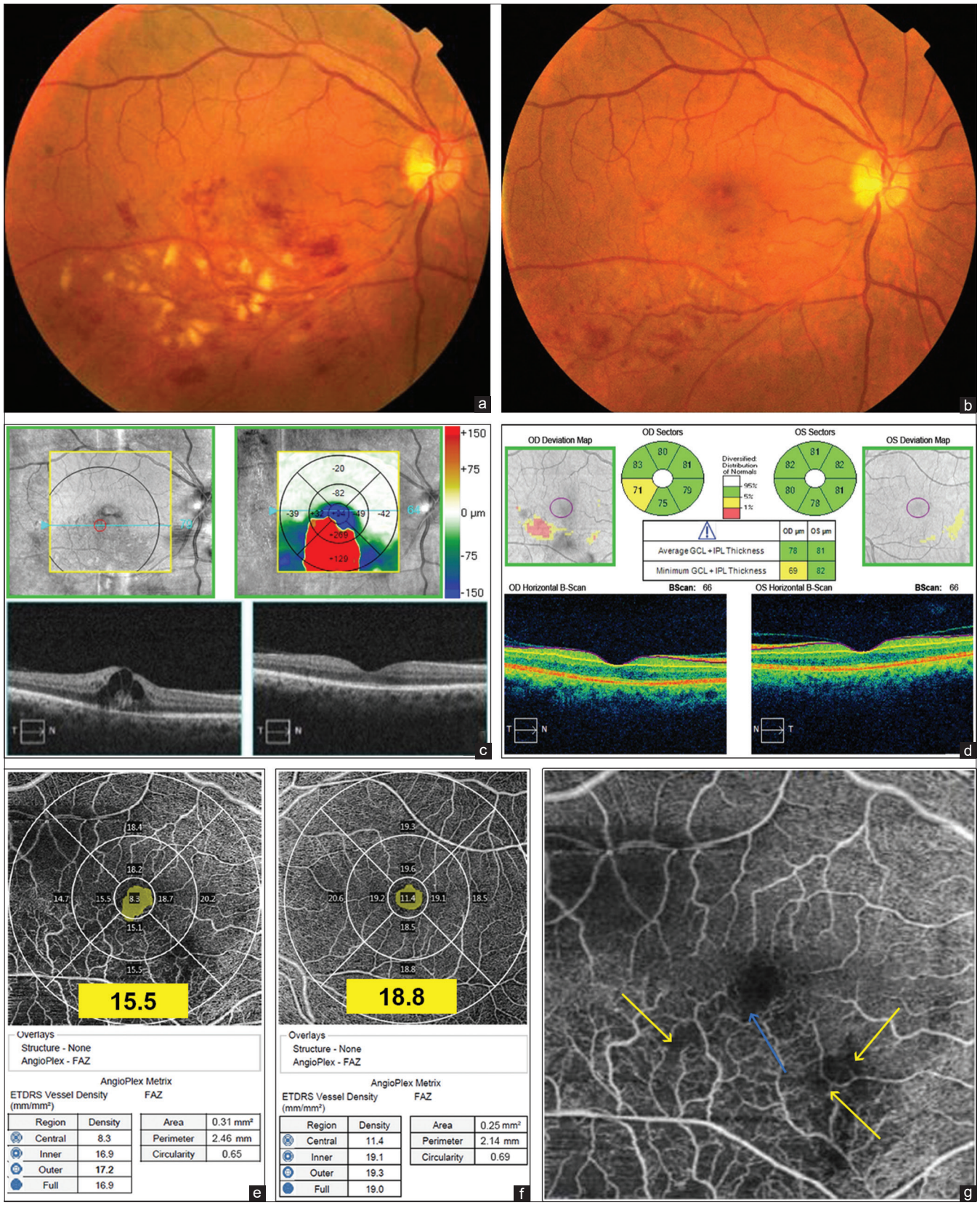

Figure 1: Color fundus-IT BRVO (a and b). Macular cube shows resolution of macular edema after three anti-VEGF injections (c). Automated ganglion cell thickness indicates thinning of ganglion cells in the IT ring (d). Automated FAZ area and circularity is found to be larger and more irregular in BRVO eye when compared with the fellow control eye on OCT A-scans (e and f). Vascular density in the outer inferior ring is less than control eye (15.5 and 18.8 mm, respectively) (g). Detailed analysis of 6 × 6mm retina slab of OCT angiography shows areas of decreased capillary flow with irregular FAZ

mean 6 × 6 mm VD was 15.86 ± 1.65 in BRVO eyes compared with 16.61 ± 2.64 in control eyes ($P = 0.15$).

Spearman's correlation test was applied to quantitative OCTA parameters of the BRVO eyes ($n = 32$) – FAZ area, GCL thickness, and average VD with VA. We did not find a significant correlation between VA and FAZ area ($\rho = 0.16$, $P = 0.34$), average GCL thickness ($\rho = 0.09$, $P = 0.6$), or VD ($\rho = 0.11$, $P = 0.49$) [Table 4]. Differences among FAZ area, circularity, GCL thickness, and VD in BRVO and control eyes are provided in Table 4.

Discussion

We used OCTA and OCT-derived anatomic measurements to determine whether GCL is correlated to microvascular damage as assessed by OCTA in BRVO eyes with resolved CME [Fig. 1a-c], and whether FAZ area, VD, and GCL thickness are significant predictors of VA in BRVO. Although statistical evaluations demonstrated consistent findings, we emphasize that the strength of our conclusions is modulated by the limited sample size of our cohort. The major findings of this study are as follows: FAZ area is larger and more irregular in BRVO eyes when compared with control eyes. FAZ area is significantly correlated with GCL thickness in BRVO. On comparison of the affected quadrant with the unaffected quadrant in BRVO eyes, the affected quadrant had a lower outer PD ($P = 0.04$), outer VD ($P = 0.036$), and GCL thickness ($P = 0.02$). There was no significant correlation of VA with FAZ, VD, or GCL thickness ($P > 0.05$) [Fig. 1].

The quantitative parameters suggestive of micovascular and neurodegeneration in BRVO following resolution of CME may help explain why some eyes may have poor visual recovery has been reported despite complete resolution of CME in BRVO.[2]

Parodi *et al*. also used FFA techniques to compare FAZ area between 20 patients with BRVO and 41 control subjects.[22] Their study has also reported that the mean FAZ area was shown to be greater in eyes with BRVO compared with controls and also showed that VA impairment due to BRVO was correlated with FAZ enlargement.

OCTA is a relatively new imaging modality that uses flow properties within a defined volume of tissue to visualize vascular structures and therefore obviates dye administration.[23] There have been a considerable number of recent studies that have reported the spectrum of retinal vascular changes due to diabetic retinopathy, BRVO, and CRVO using OCTA.[11,24] With regard to quantitative evaluation, recent evidence also suggests that OCTA is a reliable technique for measuring FAZ area that compares favorably to histology.

Table 4: Correlation of FAZ area, GCL thickness, vessel density with VA in BRVO eyes

Parameter	Correlation (ρ)*	P
FAZ area	0.16	0.34
GCL thickness	0.09	0.6
Average VD	0.11	0.49

FAZ=Foveal avascular zone; GCL=Ganglion cell layer; VA=Visual acuity; BRVO=Branch retinal vein occlusion; VD=Vessel density. *Spearman's correlation test

Samara *et al*. evaluated eyes BRVO and compared FAZ area measurements between the eye with BRVO and the fellow normal eye from the same subject.[20] They found that FAZ area in BRVO was significantly enlarged at the level of the deep capillary network only. We observed an enlargement of the FAZ in the SCP using an automated analysis.

Most of the studies using OCTA have examined the association between FAZ size and VA and omitted the influence of neuronal damage.[18,20,24,25] Our results also suggest that ischemic area of the SCP seems to be related to a decreased thickness of inner retina, as it was correlated with the area of decreased GCL layer thickness. Similar results were reported by Basílio *et al*., but in their study to determine the ischemic area in superficial and deep plexus, the area of capillary density loss was delimited using an additional software Sketch and CalcTM Software and VD and FAZ was not quantified.[26] Our study is also in keeping with Lim *et al*. who concluded that the thickness of macula, GCL-IPL, and retinal nerve fiber layer (RNFL) in the ischemic BRVO group was significantly reduced compared with the nonischemic BRVO group, especially in the RNFL.[27] However, we did not use FFA to delineate two groups of BRVO.

Yu *et al*. showed that the inner retina was rendered relatively anoxic following experimental retinal arterial occlusion, thereby providing evidence that vasculogenic insults to the fovea perturb the delicate balance between oxygen supply and consumption within the inner retina.[28] Because the choroid is unable to sufficiently oxygenate the inner retina following retinal vascular injury, it is plausible that FAZ size, and therefore the area of the macula devoid of a retinal blood supply, would correlate to the degree of visual dysfunction in diabetic retinopathy and BRVO. In diabetic retinae of animal models, glial cells (prominently at the RNFL) and RGCs have shown an increased expression of vascular endothelial growth factor (VEGF).[29] As a result, the excessive level of VEGF promotes breakdown of the blood–retinal barrier, and thus allows entry of circulatory harmful agents into the neuronal retina.[30]

As reported in diabetic retinopathy studies previously,[31-33] we hypothesize that mechanisms of neuroretinal degeneration and microvascular changes might be pathologically linked in BRVO as well as further studies are necessary to corroborate this relationship.

The limitations of this study include its retrospective design, nonstandardized treatment protocol for treating macular edema, and the lack of preoperative OCTA information, which is important but often difficult to accurately assess in the presence of CME. In addition, we could analyze only a limited area (6 × 6 mm) of retinal perfusion, which is important for central vision but may not reflect the whole disease process in BRVO.

Conclusion

In summary, the FAZ is more irregular and enlarged in eyes with BRVO and GCL is thinner, especially in the affected quadrant suggesting neuronal degeneration as a sequela of BRVO. In addition, both perfusion and VD are reduced in the quadrant affected by the BRVO demonstrating regional quantitative differences in the retinal microvasculature.

These parameters may prove useful in monitoring the disease progression and treatment response.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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