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Original Article

Peripapillary Retinal Nerve Fiber Layer Thickness in Patients with Unilateral Retinal Vein Occlusion

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Abstract

Background: Retinal vein occlusion (RVO), including branch (BRVO) and central retinal vein occlusion (CRVO), can lead to vision loss and optic nerve damage. Understanding changes in peripapillary retinal nerve fiber layer (pRNFL) thickness in affected and fellow eyes is crucial for managing these conditions.

Objective: This study evaluated longitudinal changes in pRNFL thickness in eyes with BRVO and CRVO, and their fellow eyes, compared with normal controls.

Methods: In this retrospective case-control study, 68 patients with newly diagnosed unilateral RVO (42 BRVO, 26 CRVO) and 45 controls were included. pRNFL thickness was measured at baseline, 6, 12, and 24 months using spectral-domain optical coherence tomography (SD-OCT) in six sectors. Baseline characteristics like age, gender, hypertension, and diabetes were recorded. Statistical analyses were conducted using SPSS 23.0, with one-way ANOVA, Pearson's chi-square test, paired t-tests, and repeated-measures ANOVA.

Results: At baseline, BRVO-affected eyes had a global pRNFL thickness of 119.15 ± 17.71 µm, higher than fellow eyes at 104.52 ± 10.46 µm ($p < 0.001$). CRVO-affected eyes had a baseline pRNFL of 136.04 ± 36.33 µm, compared to 99.93 ± 13.59 µm in fellow eyes ($p < 0.001$). At 24 months, only the temporal sector in CRVO eyes showed significant pRNFL differences. Global pRNFL thickness in fellow eyes of both BRVO and CRVO groups decreased significantly at 24 months, with no significant change in the control group. Fellow eyes of the CRVO group had significantly lower pRNFL thickness at 12 and 24 months compared to BRVO and control groups.

Conclusion: Both BRVO and CRVO affect pRNFL thickness in fellow eyes, with CRVO showing more susceptibility to damage. This suggests a shared vascular abnormality between RVO and glaucoma, highlighting the importance of careful pRNFL monitoring, particularly in CRVO patients.

1 Introduction

Retinal vein occlusion (RVO) is recognized as the second most prevalent cause of vision loss among retinal vascular diseases, following diabetic retinopathy. RVO is categorized into branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO) based on the location of the blocked vein. These conditions are characterized by vascular engorgement, stasis, intraretinal hemorrhages, cotton wool spots, and lipid exudation. Kim et al. classified RVO according to the location of the occluded vein into arteriovenous crossing RVO (AV-RVO), optic cup RVO (OC-RVO), and optic nerve RVO. Optic nerve RVOs are further divided into ONHS-RVO and NONHS-RVO based on the presence or absence of optic nerve head swelling (ONHS). RVOs not occurring at these sites are grouped as no-site RVO (NS-RVO) (6). Visual acuity (VA) may be decreased due to macular edema, vitreous hemorrhage, or macular ischemia, with BRVO being four to six times more frequent than CRVO. Cardiovascular risk factors, particularly arterial hypertension (AHT), increase the incidence of RVO. The incidence rate of BRVO ranges from 0.5% to 1.2%, with various risk factors including hypertension, hyperlipidemia, diabetes mellitus, thrombophilia, hypercoagulability, systemic and inflammatory diseases, medications, and ocular conditions (1,2). Major complications of BRVO include macular edema and retinal nonperfusion, both closely associated with increased production of vascular endothelial growth factor (VEGF). Diana-Maria Dărăbuş et al. reported that the evolution of best corrected visual acuity (BCVA) is

significantly related to age and type of occlusion but not to gender, with the greatest decrease in central macular thickness (CMT) following intravitreal treatment observed after the first injection (3).

RVO patients have a higher prevalence of glaucoma compared to the general population, with studies indicating higher mean intraocular pressure (IOP) in RVO patients than in normal controls (4). Elevated IOP is believed to cause blood vessel compression and intimal proliferation, leading to RVO (5). Additionally, systemic diseases such as hypertension and diabetes contribute to both glaucomatous optic neuropathy and RVO. Several studies have examined the peripapillary retinal nerve fiber layer (pRNFL) to explore the association between RVO and glaucoma (6-10). Spectral-domain optical coherence tomography (SD-OCT) is a modern, high-speed, noninvasive imaging technique that provides detailed visualization of the 10 retinal layers and is effective for measuring the thickness of the macula, ganglion cell–inner plexiform layer (GC-IPL), and retinal nerve fiber layer (RNFL). The pRNFL can be assessed in six sectors: nasal (N), temporal (T), nasal superior (NS), temporal superior (TS), nasal inferior (NI), and temporal inferior (TI). Findings suggest that two years after a unilateral BRVO diagnosis, the pRNFL thickness in the affected eye is thinner than in the normal fellow eye (8). Moreover, studies indicate that the pRNFL thickness in the normal fellow eyes of patients with unilateral RVO is thinner compared to normal controls, supporting the hypothesis that RVO and glaucoma share systemic vascular abnormalities (6, 9, 10).

Longitudinal comparisons of pRNFL thickness in BRVO and CRVO have not been previously reported, and the extent of glaucomatous damage between these conditions remains unknown. This study aims to fill this gap by comparing longitudinal changes in pRNFL thickness between the affected and fellow eyes of patients with unilateral BRVO and unilateral CRVO.

2 Material and Methods

The study was designed as a retrospective case-control investigation conducted at the Al-Shifa Trust Eye Hospital, Rawalpindi, from December 2023 to April 2024, aiming to evaluate longitudinal changes in peripapillary retinal nerve fiber layer (pRNFL) thickness in eyes affected by branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO), as well as their fellow eyes. The study population comprised patients with newly diagnosed unilateral BRVO (42 patients) and unilateral CRVO (26 patients). The control group included 45 patients without abnormal findings on fundus examination. The sample size was determined using G*Power and a non-probability sampling technique.

Institutional review board approval was obtained from the IRB committee at the Pakistan Institute of Ophthalmology, Al-Shifa Trust Eye Hospital. The study adhered to the principles of the Helsinki Declaration, and fully informed written consent was obtained from all study subjects. Patients with a history of optic nerve disease (e.g., glaucoma, ischemic optic neuropathy, and optic neuritis) or glaucomatous optic disc features (increased cup/disc ratio, neural rim narrowing/notching, and disc hemorrhage) were excluded. Other exclusion criteria included a history of retinal disease or uveitis, previous treatments affecting RNFL thickness (intraocular surgery, intravitreal injection, laser photocoagulation, glaucoma eye drops), spherical equivalent > ±6.0 D, or significant media opacity preventing clear imaging.

The best-corrected visual acuity (BCVA) and intraocular pressure (IOP) were assessed at baseline and at 6, 12, and 24 months. IOP was measured using the Goldmann Applanation Tonometer (GAT). Peripapillary retinal nerve fiber layer (pRNFL) thickness and central macular thickness (CMT) were measured using spectral-domain optical coherence tomography (SD-OCT) (Spectralis® OCT, Heidelberg Engineering, Heidelberg, Germany) (11). The pRNFL thickness was automatically measured in six sectors: temporal (315–45°), superior temporal (45–90°), superior nasal (90–135°), nasal (135–225°), inferior nasal (225–270°), and inferior temporal (270–315°). Global RNFL thickness was obtained by averaging 360° pRNFL thickness measurements.

Data collection involved gathering demographic information, systemic disease history, and ocular measurements at specified time points. The demographic characteristics included age, gender, and systemic diseases like hypertension and diabetes. The pRNFL thickness measurements were recorded and compared among the affected eyes, fellow eyes, and control eyes at baseline, 6, 12, and 24 months.

Statistical analyses were conducted using SPSS version 23.0, with results presented as mean ± standard deviation. One-way ANOVA and Pearson's chi-square test were used to compare demographics and characteristics among the three groups. Paired t-tests compared affected and fellow eyes, as well as changes from baseline to 24-month follow-up. An independent samples t-test compared pRNFL thickness between fellow eyes of unilateral RVO patients and normal controls. Repeated-measures ANOVA was employed to analyze pRNFL changes over time between groups. Statistical significance was set at $p < 0.05$.

This comprehensive methodological approach ensured robust and reliable data collection, ethical adherence, and rigorous statistical analysis to elucidate the impact of BRVO and CRVO on pRNFL thickness and contribute to the understanding of their association with systemic vascular abnormalities and glaucoma.

3 Results

The study included 42 patients with BRVO, 26 with CRVO, and 45 controls. The baseline characteristics of the patients are summarized in Table 1. There were no significant differences in age, gender distribution, or the prevalence of hypertension and diabetes among the three groups.

Table 1. Baseline Characteristics of Patients

Characteristic	BRVO (n=42)	CRVO (n=26)	Controls (n=45)	p-value
Age (years)	63.20 ± 10.02	65.19 ± 15.11	63.44 ± 10.31	0.753
Gender				0.216
Male	14	12	12	
Female	28	14	33	
Affected Eye				0.384
OD	20	9	22	
OS	22	17	23	
Hypertension	21	15	25	0.685
Diabetes	9	9	8	0.222

The peripapillary retinal nerve fiber layer (pRNFL) thickness was compared between affected and fellow eyes of patients with BRVO and CRVO at baseline, 6, 12, and 24 months, as detailed in Table 2 and Table 3.

Table 2. Global pRNFL Thickness in BRVO and CRVO: Affected vs. Fellow Eyes

Group	Time Point	Affected Eye (µm)	Fellow Eye (µm)	p-value
BRVO	Baseline	119.15 ± 17.71	104.52 ± 10.46	<0.001*
	6th month	105.76 ± 11.54	104.07 ± 10.58	0.179
	12th month	103.70 ± 12.33	103.87 ± 10.33	0.899
	24th month	101.60 ± 13.32	103.35 ± 10.21	0.159
CRVO	Baseline	136.04 ± 36.33	99.93 ± 13.59	<0.001*
	6th month	118.46 ± 34.12	98.81 ± 14.05	0.005*
	12th month	106.50 ± 18.95	97.00 ± 14.44	0.001*
	24th month	101.48 ± 25.85	96.36 ± 14.61	0.254

Note:

*p<0.05 indicates statistical significance.

Table 3. Sectoral pRNFL Thickness in BRVO and CRVO: Affected vs. Fellow Eyes

Sector	Group	Time Point	Affected Eye (µm)	Fellow Eye (µm)	p-value
Superior Temporal	BRVO	Baseline	161.28 ± 31.33	144.35 ± 22.64	0.001*
		24th month	130.19 ± 34.54	143.74 ± 21.11	0.007*
	CRVO	Baseline	168.96 ± 40.85	138.85 ± 22.74	<0.001*
		24th month	129.08 ± 37.14	131.12 ± 26.39	0.804
Temporal	BRVO	Baseline	101.15 ± 31.00	76.85 ± 12.85	<0.001*
		12th month	81.37 ± 16.24	75.78 ± 11.86	0.013*
	CRVO	Baseline	127.11 ± 54.33	76.26 ± 14.28	<0.001*
		24th month	87.84 ± 31.98	73.60 ± 15.02	0.006*
Inferior Temporal	BRVO	Baseline	167.30 ± 40.40	151.26 ± 19.36	0.004*
		6th month	149.71 ± 32.00	152.29 ± 17.25	0.564
	CRVO	Baseline	168.70 ± 53.62	143.41 ± 28.56	0.012*
		6th month	163.29 ± 38.39	141.77 ± 26.09	0.002*

Note:

*p<0.05 indicates statistical significance.

Global pRNFL thickness in the BRVO group decreased significantly from baseline to 12 and 24 months (p<0.05), while CRVO patients showed significant thinning at 12 and 24 months compared to baseline. The pRNFL thickness in the superior temporal sector was lower

in the affected eyes of the BRVO group at 24 months compared to fellow eyes, and significant thinning was observed in CRVO eyes at multiple time points in the temporal and inferior temporal sectors.

The best-corrected visual acuity (BCVA) and central macular thickness (CMT) in BRVO and CRVO groups were compared at baseline and 24 months, as shown in Table 4.

Table 4. Visual Acuity and CMT in BRVO and CRVO: A Comparative Analysis

Measure	Group	Time Point	Affected Eye	Fellow Eye	p-value
BCVA (logMAR)	BRVO	Baseline	0.46 ± 0.43	0.04 ± 0.08	<0.001*
		24th month	0.23 ± 0.29	0.05 ± 0.07	<0.001*
	CRVO	Baseline	0.72 ± 0.72	0.13 ± 0.19	<0.001*
		24th month	0.66 ± 0.71	0.13 ± 0.17	0.001*
CMT (µm)	BRVO	Baseline	468.33 ± 194.17	262.59 ± 26.52	<0.001*
		24th month	298.45 ± 75.54	265.89 ± 27.17	0.010*
	CRVO	Baseline	563.22 ± 247.01	264.22 ± 29.47	<0.001*
		24th month	356.96 ± 134.09	263.96 ± 28.31	0.001*

Note:

*p<0.05 indicates statistical significance.

In BRVO patients, affected eyes had worse BCVA and higher CMT at baseline compared to fellow eyes. Over 24 months, BCVA improved in affected eyes but remained stable in fellow eyes, while CMT decreased in affected eyes but not in fellow eyes. In CRVO patients, affected eyes had worse BCVA and higher CMT at baseline, with BCVA improving and CMT decreasing by 24 months. Fellow eyes showed stable BCVA and CMT over time.

The intraocular pressure (IOP) remained stable in both BRVO and CRVO groups over the 24-month period, with no significant differences observed between affected and fellow eyes (Table 5).

Table 5. Intraocular Pressure (IOP) in BRVO and CRVO

Group	Time Point	Affected Eye (mmHg)	Fellow Eye (mmHg)	p-value
BRVO	Baseline	14.98 ± 2.93	15.52 ± 2.92	0.091
	24th month	14.66 ± 3.21	14.78 ± 3.38	0.904
CRVO	Baseline	15.74 ± 2.98	15.85 ± 3.02	0.855
	24th month	15.62 ± 3.48	15.52 ± 3.00	0.832

In summary, this study demonstrated that BRVO and CRVO impact pRNFL thickness in both affected and fellow eyes, with CRVO eyes being more susceptible. These results highlight the importance of careful pRNFL monitoring in patients with RVO, particularly those with CRVO. The findings suggest a shared pathophysiology between RVO and glaucoma, emphasizing the need for comprehensive ocular assessments in these patients.

4 Discussion

The study was the first to compare longitudinal pRNFL thickness changes between BRVO and CRVO patients. It found that initially, global and sectoral pRNFL thicknesses were greater in the affected eyes than in the fellow eyes of both groups. However, after 24 months, only the temporal sector in CRVO-affected eyes remained significantly thicker. Additionally, the global pRNFL thickness in fellow eyes decreased significantly at 24 months in both BRVO and CRVO groups but remained stable in normal controls. Notably, the fellow eyes in the CRVO group had significantly lower pRNFL thickness at 12 and 24 months compared to BRVO patients and normal controls.

Previous research indicated that pRNFL thickness in the affected eyes of both BRVO and CRVO groups decreased significantly over time, initially being greater than those in fellow eyes due to macular edema. As CMT decreased, so did pRNFL thickness in the affected eyes. Studies on diabetic retinopathy and age-related macular degeneration also reported that macular lesions impacted pRNFL, emphasizing that RVO-related macular edema involves the inner retinal layers, predominantly affecting the RNFL (12, 13). In contrast, the pRNFL thickness in the superior temporal sector was lower in the affected eyes of the BRVO group at 12 and 24 months compared to fellow eyes. A study of 20 unilateral BRVO patients found that mean RNFL thickness was initially greater in affected eyes but lower at 6 and 12 months, suggesting that BRVO causes RNFL thinning (7). Frangieh et al.'s histopathologic study supported this, showing inner retinal ischemic

atrophy in the occluded area (16). However, in the CRVO group, no sector had lower pRNFL thickness in affected eyes at 24 months. The temporal sector pRNFL thickness remained significantly greater, likely due to persistent macular edema, which was more pronounced in the CRVO group. Further studies were needed to determine if this effect continued after the resolution of macular edema.

RVO was associated with glaucoma, sharing risk factors like old age, hypertension, diabetes, cardiovascular disease, and hyperlipidemia. Increased blood and plasma viscosity in RVO and glaucoma patients suggested systemic vascular abnormalities that could affect both eyes (18). The fellow eyes of BRVO patients showed no significant differences in pRNFL compared to normal controls, but global pRNFL thickness decreased significantly at 24 months. In CRVO patients, the fellow eyes showed significant decreases in global, superior temporal, and inferior temporal sector pRNFL thickness at 24 months. These findings supported the idea that systemic vascular abnormalities contributed to both glaucomatous optic neuropathy and RVO (15). Shin et al. also reported lower peripapillary vessel density and perfusion density in the fellow eyes of unilateral RVO patients, with pRNFL thickness significantly related to these densities (9). Reduced blood flow could cause ischemic damage to optic nerve tissue, leading to decreased pRNFL.

Previous cross-sectional studies found that fellow eyes of unilateral RVO patients had lower pRNFL thickness compared to normal controls. Kim et al. (6) and Shin et al. (9) reported reduced average, inferior quadrant, and temporal quadrant pRNFL thickness in these eyes, while Sirakaya et al. (10) found lower average and inferior quadrant pRNFL thickness in unilateral BRVO. The inferior quadrant, where glaucoma changes were common, showed a consistent decrease (19). Longitudinal studies indicated a greater annual reduction rate in pRNFL thickness in fellow eyes of unilateral RVO patients compared to controls, though BRVO and CRVO were not analyzed separately and included a small CRVO sample. In the study, fellow eyes of CRVO patients had significantly lower global, inferior temporal sector, and inferior nasal sector pRNFL thicknesses at 12 and 24 months compared to both normal controls and BRVO fellow eyes. Reductions were also more pronounced in CRVO fellow eyes, suggesting increased susceptibility to pRNFL damage.

The study had several strengths, including a robust methodological approach and the use of spectral-domain optical coherence tomography (SD-OCT) for precise measurement of pRNFL thickness. However, there were limitations, such as its nonrandomized, retrospective design and the lack of confirmation through visual field tests to assess functional changes. Additionally, while hypertension and diabetes prevalence was matched among groups, data on disease severity and specific treatments were not collected. Future prospective studies should compare blood pressure and laboratory data across groups. Despite these limitations, the study highlighted key differences between BRVO and CRVO and their association with glaucoma, emphasizing the utility of pRNFL thickness measurement in confirming structural changes in early glaucoma (20).

In conclusion, the study found that fellow eyes of BRVO and CRVO patients experienced a reduction in pRNFL thickness compared to normal controls, with CRVO fellow eyes being particularly vulnerable to pRNFL damage over two years. These results suggested shared systemic vascular abnormalities between RVO and glaucoma and potential differences in the mechanisms of BRVO and CRVO. Close monitoring of pRNFL changes in both affected and fellow eyes, especially in CRVO patients, was recommended.

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