

# Changes in peripapillary microvasculature and retinal thickness in the fellow eyes of patients with unilateral retinal vein occlusion: An OCTA study



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**Received:** 24-May-2023, Manuscript No. FMDM-23-99788; **Editor assigned:** 26-May-2023, PreQC No. FMDM-23-99788 (PQ); **Reviewed:** 09-Jun-2023, QC No. FMDM-23-99788; **Revised:** 24-Jul-2023, Manuscript No. FMDM-23-99788 (R); **Published:** 31-Jul-2023, DOI: 10.37532/1758-1907.2023.13(5).520-526

## Abstract

**Background:** Retinal Vein Occlusion (RVO) is the second most common retinal vascular disease following diabetic retinopathy and is a frequent cause of significant visual loss and associated morbidity.

**Aim and objectives:** To assess peripapillary Vessel Density (VD), Retinal Nerve Fiber Layer (RNFL) and Ganglion Cell Complex (GCC) in the fellow eyes of patients with unilateral Retinal Vein Occlusion (RVO) (either CRVO or BRVO) using Optical Coherence Tomography Angiography (OCTA) and compare it with controls.

**Subjects and methods:** This is an observational study that will be conducted on (25) patients with unilateral RVO (either CRVO or BRVO) and (25) normal controls chosen from outpatient clinic.

**Results:** The RNFL thicknesses in the fellow eyes of RVO patients was significantly thinner than in normal controls. VD of radial peripapillary plexus and ganglion cell complex thickness were slightly lower than those of controls.

**Conclusion:** OCTA revealed that RNFL thickness in the fellow eyes of patients with unilateral RVO was significantly decreased, lower peripapillary VD and GCC thickness were also observed compared to healthy controls.

## Introduction

Retinal Vein Occlusion (RVO) is the second most common retinal vascular disease following diabetic retinopathy and is a frequent cause of significant visual loss and associated morbidity, which increases with age and reported a prevalence of approximately 0.7%–1.6% [1].

Various systemic diseases, such as Hypertension (HTN), diabetes, arteriosclerosis and hyperlipidemia are considered to be risk factors for the development of RVO [2]. Many studies

have found an association between RVO and glaucoma and increased Intraocular Pressure (IOP) [3].

In 1913, Verhoeff first postulated that elevated IOP collapses and compresses the wall of the retinal vein, causing intimal proliferation in the vein. An ocular HTN study reported that a larger horizontal cup to disc ratio was associated with the development of RVO [4].

Angiography has been part of the diagnostic work up of RVOs. A major aim of these evaluations

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**KEYWORDS**

- retinal nerve fiber layer
- ganglion cell inner plexiform layer
- retinal vein occlusion
- peripapillary OCTA
- vessel density
- perfusion density
- fellow eye

is to delineate the area of the ischemic retina. Fluorescein Angiography (FA), the standard method, can show ischemic areas in both the central and peripheral retina and these images have been used for both prognostication and treatment decisions in cases of RVOs. However, FA may not always yield clear images of the Foveal Avascular Zone (FAZ), whose intactness has prognostic value [5].

In recent reports, a decrease in peripapillary microvascular perfusion using OCTA was associated with glaucoma [6].

Kim, et al. reported that Retinal Nerve Fiber Layer (RNFL) thickness decreased in the fellow eyes of unilateral RVO patients and that RVO and glaucoma may share systemic risk factors, reflecting a common pathogenic mechanism, such as systemic HTN, diabetes mellitus and arteriosclerosis. There are several studies on changes in foveal micro vascular perfusion in the fellow eyes of RVO patients with OCTA.

Aim of the work was to assess peripapillary Vessel Density (VD), Retinal Nerve Fiber Layer (RNFL) and Ganglion Cell Complex (GCC) in the fellow eyes of patients with unilateral Retinal Vein Occlusion (RVO) (either crvo or brvo) using Optical Coherence Tomography Angiography (OCTA) and compare it with controls.

**Materials and Methods**

This is an observational case control study that will be conducted on patients with unilateral RVO (either crvo or brvo) and normal controls chosen from outpatient clinic.

**The exclusion criteria:** In the fellow eyes and controls were as follows: A history of retinal or optic nerve diseases or glaucoma; a Best Corrected Visual Acuity (BCVA) <6/12; high myopia (spherical equivalent) >6 diopters, axial length >26 mm and significant media opacity.

**Methods:** All patients were undergoing.

**Ophthalmological examination as following:** BCVA using a Snellen chart, IOP and slit-lamp biomicroscopy, dilated fundus examination.

**OCTA scans acquired:** Vessel Density (VD) of radial Peripapillary plexus calculated *via* 4.5 × 4.5 mm optic disc scans centered on the optic disc. RNFL calculated *via* 3.45 mm circle scans centered on the optic disc, Ganglion Cell complex (RNFL+GC+IPL) calculated.

**Statistical analysis:** The collected data presented in tables and suitable graphs and analyzed by IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Quantitative variables will be expressed as mean ± SD, and range. Qualitative variables as frequency and percentage. The level of significance will be p<0.05.

This study does not include any data, information or images which could lead to direct identification of persons participated in this research.

**Results**

The current study included 25 patients who had RVO; 44% had right sided RVO and 56% had left RVO. Regarding other comorbidities, 14% had DM and 26% had hypertension (TABLE 1).

TABLE 1: Clinical data of the studied fellow eye population.			
		N= 25	
		N	%
Side of RVO	Right	11	44%
	Left	14	56%
DMS	No	18	72%
	Yes	7	28%
HTN	No	12	48%
	Yes	13	52%

**Independent student t test:** There is no statistically significant difference between fellow

eye and healthy controls as regard the age (TABLE 2).

**TABLE 2: Comparison of the age of the studied groups.**

		Fellow eye	Healthy controls	t	P-value	Sig.
		No.=25	No.=25			
Age (years)	Range	36-72	32-63	1.47	0.148	NS
	Mean ± SD	52.92 ± 10.41	48.64 ± 10.18			

**Note:** P-value >0.05: Non Significant (NS); P-value <0.05: Significant (S); P-value < 0.01: Highly Significant (HS)

**Independent student t test:** There is statistically significant higher IOP in fellow eye than healthy significant lower UCVA, BCVA and statistically controls (TABLE 3).

**TABLE 3: Comparison of visual acuity and IOP of the studied groups.**

	Fellow eye		Healthy controls		t	P-value	Sig.
	No.=25		No.=25				
	Mean	SD	Mean	SD			
UCVA	0.33	0.1	0.83	0.22	-10.202	0	HS
BCVA	0.75	0.22	0.99	0.07	-5.196	0	HS
IOP	14.84	1.75	13.88	1.62	2.016	0.049	S

**Note:** P-value >0.05: Non Significant (NS); P-value <0.05: Significant (S); P-value < 0.01: Highly Significant (HS)

**Independent student t test:** There is no statistically significant difference between fellow eye and healthy controls as regard the peripapillary, RPCP sup and RPCP information (TABLE 4).

**TABLE 4: Comparison of the RPC of the studied groups.**

	Fellow eye		Healthy controls		t	P-value	Sig.
	No.=25		No.=25				
	Mean	SD	Mean	SD			
Peripapillary	50.82	3.42	51.85	1.52	-1.366	0.178	NS
RPCP sup	51.01	3.27	52.29	1.34	-1.81	0.077	NS
RPCP inf	50.61	4.03	51.57	2.26	-1.043	0.302	NS

**Note:** P-value >0.05: Non Significant (NS); P-value <0.05: Significant (S); P-value < 0.01: Highly Significant (HS)

**Independent student t test:** There is statistically insignificant difference in RPCP in the four quadrants in between fellow eye and healthy controls (TABLE 5).

**TABLE 5: Comparison of the RPC quadrants of the studied groups.**

	Fellow eye		Healthy controls		t	P-value	Sig.
	No.=25		No.=25				
	Mean	SD	Mean	SD			
RPCP nasal	48.96	13.73	52.24	1.9	1.183	0.242	NS
RPCP sup	50.64	4.2	51.16	2.64	-0.524	0.603	NS
RPCP temp	54.2	3.91	55.24	2.17	-1.165	0.25	NS
RPCP inf	52.08	3.51	52.6	2.5	-0.603	0.549	NS

**Note:** P-value >0.05: Non Significant (NS); P-value <0.05: Significant (S); P-value < 0.01: Highly Significant (HS)

**Independent student t test:** There is statistically significant lower RNFL in fellow eye than healthy controls as regard the average RNFL, superior half RNFL and inferior half RNFL (TABLE 6).

**TABLE 6: Comparison of the RNFL of the studied groups..**

	Fellow eye		Healthy controls		t	P-value	Sig.
	No.=25		No.=25				
	Mean	SD	Mean	SD			
Average RNFL	96.96	8.11	106.48	12.73	-3.154	0.003	HS
Superior RNFL	99.92	8.78	111.56	15.92	-3.201	0.002	HS
Inferior RNFL	93.16	10.96	101.32	10.52	-2.685	0.01	HS

**Note:** p-value >0.05: Non Significant (NS); P-value <0.05: Significant (S); P-value< 0.01: Highly Significant (HS)

**Independent student t test:** There is statistically significant lower RNFL in the four quadrants in fellow eye than healthy controls (TABLE 7).

**TABLE 7: Comparison of the RPC quadrants of the studied groups.**

	Fellow eye		Healthy controls		t	P-value	Sig.
	No.=25		No.=25				
	Mean	SD	Mean	SD			
RPCP nasal	48.96	13.73	52.24	1.9	1.183	0.242	NS
RPCP sup	50.64	4.2	51.16	2.64	-0.524	0.603	NS
RPCP temp	54.2	3.91	55.24	2.17	-1.165	0.25	NS
RPCP inf	52.08	3.51	52.6	2.5	-0.603	0.549	NS

**Note:** P-value >0.05: Non Significant (NS); P-value <0.05: Significant (S); P-value< 0.01: Highly Significant (HS)

**Independent student t test:** There is no statistically significant difference between fellow eye and healthy controls as regard the ganglion cell complex average thickness (TABLE 8).

**TABLE 8: Comparison of the ganglion cell complex of the studied groups.**

		Fellow eye	Healthy controls	t	P-value	Sig.
		No.=25	No.=25			
Ganglion cell complex average thickness	Range	90 -110	84-105	-1.027	0.309	NS
	Mean ± SD	95.84 ± 5.02	97.44 ± 5.95			

**Note:** P-value >0.05: Non Significant (NS); P-value <0.05: Significant (S); P-value<0.01: Highly Significant (HS)

**Discussion**

Optical Coherence Tomography Angiography (OCTA) is a new noninvasive imaging tool that can be used to visualize the Radial Peripapillary Capillary (RPC) layer which is the most superficial capillary layer nourishing the RNFL surrounding the Optic Nerve Head (ONH).

The main aim of this study was to assess peripapillary Vessel Density (VD), Retinal Nerve Fiber Layer (RNFL) and Ganglion Cell Complex (GCC) in the fellow eyes of patients with unilateral Retinal Vein Occlusion (RVO) (either crvo or brvo) using Optical Coherence Tomography Angiography (OCTA) and compare it with controls.

This is an observational case control study that was conducted on patients with unilateral RVO

(either crvo or brvo) and normal controls chosen from outpatient clinic. The duration of the study ranged from 6-12 months.

The current study included 25 patients who had RVO; 44% had right sided RVO and 56% had left RVO. Regarding other comorbidities, 14% had DM and 26% had hypertension. There is no statistically significant difference between fellow eye and healthy controls as regard the age.

We have shown that the fellow eyes of RVO subjects had a thinner RNFL than did control eyes. Retinal nerve fiber layer thinning was most obvious in superior and inferior quadrants. Because these quadrants represent the area where glaucomatous structural changes are most frequently seen it may be proposed that thinning of the RNFL in the fellow eyes of patients with

RVO may be glaucomatous in nature, or that the mechanism of RNFL thinning is similar, at least in part, to that of glaucoma development [7-10].

The association between RVO and glaucoma has long been recognized. The compression and intimal proliferation of blood vessels caused by elevated IOP, or distortion of retinal vessels attributed to optic disc cupping, has been hypothesized as a potential mechanism of the association. However, it has also been suggested that the association between the two may be simply a manifestation of a common underlying vascular abnormality rather than a cause and effect relationship.

Several forms of vascular pathophysiology have been suggested as possible common mechanisms of damage in glaucoma and RVO, such as systemic hypertension and atherosclerosis [11,12]. Stewart, et al. recently suggested that dysfunctional vascular auto regulation and systemic hypertension, both of which can be caused by insulin resistance, might result in both glaucomatous optic neuropathy and RVO [13].

In subset analysis, RNFL thinning in the fellow eyes of patients with RVO was more prominent in a subgroup aged more than 60 years. It has been suggested that the mechanism of development of RVO may change with age. Thus, systemic hypertension and atherosclerotic developments may play pivotal roles in the development of RVO in elderly patients, whereas coagulation disorders and inflammation are thought to be important risk factors in younger patients with RVO. Therefore, increased thinning of the RNFL in subjects aged more than 60 years may suggest that arterial stiffness and atherosclerosis explain both RVO and thinning of the RNFL [14-16].

To investigate the association between RVO and glaucoma, it would be ideal to search for glaucomatous damage in RVO eyes. However, this is not practical, for several reasons. First, in the early stage of RVO, retinal edema may occur, leading to increases in RNFL thicknesses in the involved sectors. This may interfere with accurate measurement of RNFL thickness. Second, RNFL thickness may be decreased in sectors with RVO, which would confound any measurement of glaucomatous thinning of the RNFL. With these limitations in mind, we conducted measurements on the contralateral eyes of patients with RVO.

An RNFL defect may develop from a retinal

cotton wool spot in a patient with diabetes mellitus and systemic hypertension. Thus, although the topographic pattern of RNFL thinning in the present study was consistent with glaucomatous change, the long term implications of RNFL thinning in the fellow eyes of patients with RVO remain to be determined.

The main findings of the study revealed that

- There is no statistically significant difference between fellow eye and healthy controls as regard the age.
- There is statistically significant lower UCVA, BCVA and statistically significant higher IOP in fellow eye than healthy controls.
- There is no statistically significant difference between fellow eye and healthy controls as regard the peripapillary, RPCP superior and RPCP inferior.
- There is no statistically significant difference in RPCP in the four quadrants in between fellow eye and healthy controls.
- There is statistically significant lower RNFL in fellow eye than healthy controls as regard the average RNFL, superior half RNFL and inferior half RNFL.
- There is statistically significant lower RNFL in the four quadrants in fellow eye than healthy controls.
- There is no statistically significant difference between fellow eye and healthy controls as regard the ganglion cell complex average thickness.

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## Conclusion

OCTA revealed that RNFL thickness in the fellow eyes of patients with unilateral RVO was significantly decreased, lower peripapillary VD and GCC thickness was also observed compared to healthy controls

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## Author Contribution

All authors have a substantial contribution to the article.

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## Consent for Publication

Not applicable.

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## Availability of Data and Material

Available.

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**Competing Interests**

None.

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**Funding**

No fund.

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**Conflicts of Interest**

No conflicts of interest.

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**Ethical Considerations**

Ethical approval from ethics committee of Benha

university obtained in addition to informed consent from patients invited to participate in the research.

All methods were carried out in accordance with relevant guidelines and regulations.

All experimental protocols were approved by ethics committee of Benha university.

All authors have agreed to submit the work.

Informed consent was obtained from all subjects.

This study does not include any data, information or images which could lead to direct identification of persons participated in this research.

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