Archives of
Ophtalmological Research

Original Article

DOI: 10.51271/AOR-0011

Evaluation of choroidal vascular structure in patients with retinal vein occlusion

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Received: 10/05/2024 ◆ Accepted: 19/07/2024 ◆ Published: 26/07/2024

Cite this article: Akyüz Dursun G, Örnek N. Evaluation of choroidal vascular structure in patients with retinal vein occlusion. *Arch Ophthalmol Res.* 2024;1(3):35-39.

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ABSTRACT

Aims: To evaluate the posterior segment structures and choroidal vascularity of the eye in patients with retinal vein occlusion (RVO) using enhanced depth imaging optical coherence tomography (EDI-OCT).

Methods: Thirty-three treatment-naïve patients with RVO (19 males, 14 females) were examined by EDI-OCT. Subfoveal choroid tickness and choroidal vascularity index (CVI) were used to compare the structural characteristics of the choroid with the eyes of twenty-nine age, and gender-matched controls. EDI-OCT images were binarised using ImageJ program.

Results: Best corrected visual acuity was significantly lower in the affected eyes compared to control group (p=<0.001). Central macular thickness, subfoveal choroidal thickness, choroid stromal area, and total choroid area were found to be significantly higher in the patient group (p=<0.05). CVI was significantly lower in the patient group and no significant difference was found between the groups in terms of intraocular pressure values (p>0.05).

Conclusion: RVO causes significant edema in the choroid stromal area without any change in the choroid lumen area. This structural changes in the choroid evaluated by EDI-OCT, a non-invasive examination, may be used in the diagnosis and follow-up of RVO.

Keywords: Retinal vein occlusion, subfoveal choroid thickness, choroid vascularity index

INTRODUCTION

Retinal vein occlusion (RVO) is the most common retinal vascular disease after diabetic retinopathy.[1] Branch RVO is significantly more common than central RVO, with a fivefold prevalence. The prevalence of RVO in adults is reported at 0.5%.[2,3] Systemic conditions such as hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HL), atherosclerosis and hyperviscosity syndrome play a role in the pathogenesis.[4,5]

The hemodynamics of the choroidal circulation are not fully understood. The role of the choroid, whose main function is to supply nutrients to the outer retinal layers, in the pathogenesis of ocular diseases is well known, but conflicting results have been reported in studies evaluating the choroid and choriocapillaris in RVO.[6-9]

Advances in imaging techniques have allowed us to examine the structural features of the retina and choroid more precisely. In particular, the enhanced depth mode of optical coherence tomography (OCT) allowed us to gain insight into the segmentation and functional status of choroidal layers.

The aim of this study was to investigate the structural changes of the choroid and the choroidal vascularity index in patients with RVO by using the enhanced depth imaging OCT (EDI-OCT).

METHODS

This study was conducted at Kırıkkale University, Faculty of Medicine, Ophthalmology Department according to the principles of the Declaration of Helsinki. EDI-OCT scans were retrieved from the database of the Ophthalmology Department of Kırıkkale University, Faculty of Medicine. Ethical approval for the study was received from the Kırıkkale University Clinical Researches Ethics Committee. (Date: 10.02.2022, Decision No: 03/01). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Subjects

This study was conducted retrospectively. A total of 33 patients (19 males, 14 females) with unilateral central or

branch RVO diagnosed between January 2021 and January 2022 were included in the study. 29 age- and gender-matched volunteers were included as the control group.

Best-corrected visual acuity (BCVA) with Snellen chart, intraocular pressure with pneumotonometer, and EDI-OCT findings (Heidelberg Engineering, Heidelberg, Germany), in which we obtained choroidal measuruments, were recorded.

RVO was diagnosed by OCT and fundus fluorescein angiography (FFA) after detailed history and fundus examination. CRVO was defined as the presence of retinal hemorrhages, a telangiectatic capillary bed, and a dilated venous system in all 4 quadrants. BRVO was defined as the presence of retinal hemorrhages or other biomicroscopic evidence of RVO in less than all four quadrants of the eye. The separate evaluation of occluded and non-occluded areas in patients diagnosed with RVO is schematized in Figure. Ischemic RVO was defined as the presence of >10 nonperfused retinal discs on FFA.

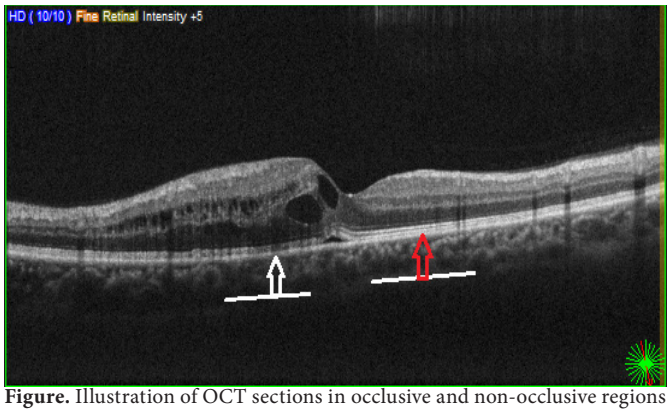

Figure. Illustration of OCT sections in occlusive and non-occlusive regions in patients with branch RVO

OCT: Optical coherence tomography, RVO: Retinal vein occlusion

The exclusion criteria were as follows: refractive errors of more than±six diopters, a history of any ocular trauma, laser treatment, intraocular injections or surgery, and poor-quality OCT images (signal strength index lower than 6 on a 10-point scale) were also excluded.

Measurements

CVI was calculated as the ratio of the area of the lumen (LA) to the total area of the choroid (TCA). For vessel lumen segmentation, the EDI-OCT images were converted to 8-bit format and thresholded using ImageJ (v1.47, NIH). Choroidal binarization followed established methods described in literatüre.[10] Color thresholding was used to further isolate luminal areas from each binarized image. Within a central 1500-µm zone, bright pixels represented the choroidal interstitium and dark pixels represented the vessel lumen.

Statistical Analysis

Statistical analyses were performed with IBM SPSS statistics, version 23.0 (SPSS Inc. Chicago, USA). Descriptive statistics, frequencies and percentages within the groups were reported as (n, %). Before analyzing the relationship between continuous variables between groups, they were subjected to normality analyses considering the number of samples in the groups (Kolmogorov-Smirnov and Shapiro-Wilk tests). Accordingly, variables with normal distribution were reported as mean±standard deviation, and variables with non-normal distribution were reported as median (minimum-maximum). Difference analysis between the two groups in terms of numerical variables was performed using the Student's t test, which compares the means for those with normal distribution, and the Mann-Whitney U test, which compares the median values for those with non-normal distribution. A value of $p<0.05$ was considered statistically significant.

RESULTS

Demographic and clinical characteristics of the groups are shown in Table 1. There was no significant difference between the groups in terms of age and gender (p=0.714, p=0.283 respectively). Body-mass index (BMI) was found to be significantly higher in the patient group than in the control group (p=<0.001).

Table 1. Demographic and clinical features of the groups

	Group 1 (RVO) (n: 33)	Group 2 (Control) (n: 29)	p Value
Age (years)	60.17±9.77	61.90±7.75	0.714¥
Gender (male/female)	19/14	13/16	0.283*
BMI (kg/m²)	32.30±6.09	25.76±3.65	<0.001
Systemic diseases			
None	1		
HT	15		
DM+HT	9		
MTHFR gene mutation	1		
Parkinson' disease	1		
Asthma	1		
HT+CAD	2		
Factor V Leiden MT	3		
Classification of RVO			
Superotemporal RVO	21		
Inferotemporal RVO	8		
Central RVO	4		
Right eye	16		
Left eye	17		
Ischemic RVO	8		
Non-ischemic RVO	25		

RVO: Retinal vein occlusion, BMI: Body-mass index, HT: Hypertension, DM: Diabetes mellitus, MTHFR: Metilentetrahidrofolat redüktaz, CAD: Coronary arter disease, ¥İndependent samples t test, *Chi-square test

The clinical features and OCT findings of the groups are shown in Table 2. BCVA was significantly lower in the affected eyes compared to the control group (p=<0.001). Central macular thickness (CMT), subfoveal choroidal thickness (SCT), stromal area of choroid (SA), and total choroid area (TCA) values were found to be significantly higher in RVO group (p=<0.05). While CVI (LA/TCA ratio) was significantly lower in the RVO group (p=<0.001), LA value was at similar

levels in both groups (p=0.607). No significant difference was found between the groups in terms of IOP values (p>0.05).

Table 2. Comparison of clinical features and OCT findings between groups

	Group 1 (n:33)	Group 2 (Control) (n:29)	p
BCVA (LogMAR)	0.2±0.25	1.00±0.00	<0.001
IOP (mmHg)	15.4±3.8	16.30±2.9	0.845
CMT	560.24±241.50	229.42±15.62	<0.001
SCT	352.45±44.64	277.79±28.29	<0.001
LA	0.38±0.04	0.39±0.06	0.607
SA	0.26±0.03	0.19±0.02	<0.001
TCA	0.64±0.07	0.58±0.08	0.003
CVI	60.80±1.39	68.60±1.37	<0.001

OCT: Optical coherence tomography, BCVA: Best corrected visual acuity, IOP: Intraocular pressure, CMT: Central macular tickness, SCT: Subfoveal choroid tickneѕs, LA: Lumen area, SA: Stromal area, TCA: Total choroid area, CVI: Choroid vascularity index, p: Independent samples t test

Comparison of macular and choroidal thickness values in occlusive and non-occlusive regions in patients with branch RVO occlusion is shown in Table 3. It was observed that both macular and choroidal thickness values were significantly higher in the occlusive group than in the non-occlusive group (p<0.001 for each).

Table 3. Macular and choroidal thicknesses in occlusive and non-occlusive areas in branch RVO eyes

	Group 1	
	Mean±SD	P
Macular tickness, occlusive area (n:23)	640 ±139	<0.001*
Macular tickness, non-occlusive area (n:29)	286 ±17	
Choroid tickness, occlusive area (n:29)	387 ±48	<0.001*
Choroid tickness, non-occlusive area (n:29)	309 ±44	

*Dependent samples t test, RVO:Retinal vein occlusion, SD: Standard deviation

Comparison of macular and choroidal thickness values in the occlusive and non-occlusive regions between the groups is shown in Table 4. Macular and choroidal thicknesses in the occlusive and non-occlusive areas were found to be significantly higher than the control group (p<0.05 for each).

Table 4. Comparison of macula and choroid thicknesses in occlusive and nonocclusive areas with the control group

	Groups		
	Group 1 (RVO) n: 29	Group 2 (Control) n: 29	
	Mean±SD	Mean±SD	P
Macular tickness, Occlusive area	639±137	234±19	<0.001
Macular tickness, Non-occlusive area	292±18	232±12	<0.001
Choroid tickness, Occlusive area	388±48	281±32	<0.001
Choroid tickness, Non-occlusive area	308±42	280±29	0.008

RVO: Retinal vein occlusion, SD: Standard deviation, p: Independent samples t test

DISCUSSION

Choroidal thickness is the most widely used parameter for choroidal assessment but is influenced by many ocular and systemic factors such as age, gender, diurnal variation and ethnicity. Low reproducibility and reliability are the main limitations associated with central choroidal thickness (CCT). Agrawal therefore proposed CVI, a measure of the vascular status of the choroid derived from the ratio of lumen area to total choroidal area.[10] Given that it is less influenced by the aforementioned factors, CVI emerges as a potentially more stable and objective marker for assessing choroidal vascularity. It offers the possibility to ameliorate the limitations of relying solely on CCT measurements. In this paper, CVI was evaluated together with macular and choroidal thickness values in patients with RVO.

It has been shown that the prevalence of RVO increases with age and age is the most important risk factor for RVO.[3] In our study group, the mean age was 61 years, and the most common comorbidity was HT. Among the risk factors identified for RVO, age and HT are the most prominent and their high prevalence in this patient cohort further underscores its prevalence. The rate of ischemic RVO was 24% in our study, which is consistent with the literature.[11-13]

There is a lack of consensus in the evaluation of choroidal thickness in patients with RVO, although many studies have been performed. Tsuiki et al.[14] showed an increase in central choroidal thickness in new cases of RVO in comparison with the contralateral eye. Similarly, there was an increase in choroidal thickness in RVO cases compared to the contralateral eye and a decrease in central choroidal thickness after intravitreal dexamethasone implant treatment.[15,16] In contrast to these results, Du et al.[9] reported that there was no difference in choroidal thickness between eyes with RVO and fellow eyes in their study evaluating chronic RVO cases. In this study, in which we evaluated acute RVO cases, we found that choroidal thickness was higher in eyes with RVO compared with the control group.

Aribas et al.[17] reported that CVI was lower in eyes with RVO compared to healthy eyes and control group. Mitamura et al.[19] reported that eyes with RVO had higher SCT, THA, and SA values in their study using fellow eyes as controls. CVI values were lower, whereas LA values were similar. They also reported that SA and TCA were significantly decreased in the affected eyes 1, 3 and 6 months after intravitreal Avastin administration in RVO cases. Hwang et al.[18] showed that the CVI values were lower in eyes with RVO and macular edema compared to those in healthy eyes. In our study, we found that CVI was lower and SCT, TCA, and SA were higher in eyes with RVO compared to the control group. However, there was no significant difference for LA compared to the control group.

Although RVO is primarily a retinal disease, choroidal changes are likely secondary to retinal pathology. In our report, we found that increased choroidal thickness was due to SA rather than LA enlargement, and that SA enlargement was indicative of choroidal stromal edema. In contrast to other retinal diseases, SA enlargement is remarkable in RVO with macular edema. In a study, only the LA was increased along the choroid in central serous chorioretinopathy,

and both the LA and the SA were increased in diabetic retinopathy.[19] Therefore, the increase in the SA appears to be a specific marker for RVO.

No increase in choroidal thickness was found in eyes with long-term RVO without macular edema. Retinal ischemia induces the production of vascular endothelial growth factor (VEGF), a potent angiogenic factor. In chronic cases without macular edema, intraocular VEGF levels are not thought to be significantly increased.[20] Rayess et al.[21] demonstrated that patients with higher baseline choroidal thickness than healthy eyes had a better response to treatment. This supports the role of excess VEGF in the pathology of choroidal edema in acute cases.

Kim et al.[22] compared eyes with acute RVO with fellow eyes and normal controls and reported that the choroidal thickness in the region of vein occlusion was significantly greater than the choroidal thickness in non-occlusive regions. Localized extravascular fluid leakage and/or high hydrostatic pressure observed in RVO may result from damaged vascular endothelial cells, vasodilation, and increased blood flow through occluded retinal vessels. In our study, we found significantly higher macular and choroidal thicknesses in occluded regions.

Limitations

The small sample size and lack of monitoring of response to treatment can be considered limitations of this study. While our study encompassed both RVO and BRVO patients, investigating these subgroups separately with larger cohorts could yield more definitive answers to specific questions about choroidal alterations in each subtype. In addition, the fact that BMI is not similar between groups reveals BMI bias. However, our study comparing the choroidal findings and choroidal vascular index of newly diagnosed and treatment-naive RVO patients with healthy controls will make a significant contribution to the literature. We think that further studies are needed to see how these parameters will change with treatment in RVO follow-up.

CONCLUSION

The increase in choroidal thickness in eyes with RVO appears to be due to stromal edema, possibly triggered by high intraocular VEGF levels, rather than direct vascular dilatation. These structural changes in the choroid, evaluated by EDI-OCT, a non-invasive examination, can be used in the diagnosis and follow-up of RVO.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Kırıkkale University Clinical Researches Ethics Commitee (Date: 10.02.2022, Decision No: 03/01).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version. All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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