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ORIGINAL PAPER

Automated macular segmentation with spectral domain optical coherence tomography in the fellow eyes of patients with unilateral retinal vein occlusion

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Abstract

Purpose To assess the change in the macular layers in the fellow eyes of unilateral retinal vein occlusion (RVO) patients and to evaluate whether certain layers are more affected based on RVO type.

Methods This retrospective study included 87 fellow eyes of patients with unilateral RVO (26 central, 61 branch) and 105 eyes of 105 subjects without RVO. Spectral domain optical coherence tomography was used for automatized retinal segmentation. The thicknesses of retinal nerve fiber layer (RNFL), ganglion cells, inner plexiform, inner nuclear, outer plexiform, outer nuclear, photoreceptor layers, overall inner retinal layers and retinal pigment epithelium (RPE) were documented.

Results Inner plexiform layer was thinner in inferior sector in RVO group compared with the control group ($p = 0.047$). The subgroup analysis showed that the retina was thinner in RVO group compared with the controls without systemic diseases in some sectors of the following layers: inferior retina, RNFL, ganglion cell layer, inner plexiform layer, inner retinal layers and RPE ($p < 0.05$). Retinal thickness was decreased in the fellow eyes of branch RVO group compared to that in the central RVO group in the some sectors ($p < 0.05$).

Conclusions The fellow eyes of unilateral RVO patients did not show major structural differences compared with the controls; however, they revealed significant sectoral thinning in many retinal layers when compared with the eyes of healthy subjects without systemic diseases. Central macula was thinner in the fellow eyes of patients with branch RVO compared to that in central RVO.

Keywords Macular segmentation · Retinal layers · Retinal thickness · Retinal vein occlusion

Introduction

Retinal vein occlusion (RVO) is the second most common cause of impaired vision from retinal vascular disease after diabetic retinopathy [1]. It typically occurs in middle-aged and elderly individuals. The incidence of vein occlusion was reported to be 4.6% after the age of 80 years, with an increase with aging [2]. The etiology of RVO is still unclear. An external compression of the vein wall is suggested. The location of compression was reported as the level of the lamina cribrosa in central retinal vein occlusion (CRVO) and at the level of arteriovenous crossing in branch retinal vein occlusion (BRVO) [3, 4]. The major risk factors for RVO have been identified as

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increasing age, hypertension, diabetes, arteriosclerotic vascular risk factors and ocular perfusion pressure [5].

Epidemiologic studies have shown that the fellow eyes of unilateral CRVO patients have a significantly increased risk of developing RVO compared with the general population [2, 6]. It was documented that the fellow eyes of unilateral RVO patients were both electrophysiologically and structurally compromised [7–11]. Significant sectoral thinning in retinal nerve fiber layer (RNFL) was documented in the fellow eyes of unilateral BRVO patients, and in 1/5th of those fellow eyes, there was a corresponding visual field defect [7]. Late vascular leakage on ultra-widefield fluorescein angiography was found in 10% of the fellow eyes of unilateral BRVO patients [9]. In another study, adaptive optics scanning light ophthalmoscope fluorescein angiography showed lower microvascular density, whereas microperimetry revealed decreased sensitivity in the fellow eyes of unilateral CRVO patients compared to that in healthy eyes [10]. A spectral domain optical coherence tomography (SD-OCT) angiography study demonstrated decreased vascular perfusion which was more profound in the deep plexus in the fellow eyes of patients with CRVO and BRVO [11].

Those findings suggest that certain subclinical abnormalities are found in the fellow eyes of RVO patients. The analysis of those eyes might elucidate the early pathological changes in an eye with RVO and possibly help in defining signals for future occlusive events. In this study, we evaluated the macular layers using spectral domain optical coherence tomography (SD-OCT) with automatized segmentation software in the fellow eyes of unilateral RVO patients. Our aims were to find out whether the fellow eyes show subclinical structural changes compared with the control eyes, to document if certain layers are more affected in the course of the disease and to assess the association of the structural changes with the RVO type.

Materials and methods

This retrospective study was conducted upon the approval of the institutional ethical committee. The study group consisted of the fellow eyes of the patients with unilateral RVO, and the control group included the eyes of subjects who attended the clinic for regular ocular examination and had no retinal or choroidal pathologies. To be eligible for the study, all participants should have undergone a comprehensive ophthalmic examination including anterior and posterior segment examination, intraocular pressure measurement and SD-OCT scans. Exclusion criteria were having ocular diseases that affect retina/optic disk (glaucoma, macular degeneration, macular edema, epiretinal membrane, vitreomacular traction, refractive disorder greater than ± 4D, etc.), the history of ocular trauma, intraocular surgery within 4 months and intraocular inflammation. "OCT images were controlled in order to eliminate any suboptimal image including incorrect segmentation layers, blurred images due to media opacity, and all patients with suboptimal OCT images were excluded from the study.

Having systemic diseases was an exclusion criterion for the control group. Coexistent systemic diseases were documented in the study group.

SD-OCT was used for macular segmentation (Heidelberg Spectral Domain Optical Coherence Tomography; Heidelberg Engineering, Dossenheim, Germany). SD-OCT provides 40,000 A scans per second, with an optical resolution of 7 μm axially and 14 μm laterally by using a 870-nm wavelength superluminescent diode. The images were acquired in high-resolution OCT mode with a digital resolution of 3.9 μm axially and 6 μm laterally and a mean automatic real time of 30. Segmentation of the macular layers was performed automatically by segmentation application (Segmentation Technology; Heidelberg Engineering) (Fig. 1). By this application, the thicknesses of RNFL, ganglion, inner plexiform, inner nuclear, outer plexiform, outer nuclear and photoreceptor layers, inner retina (the layers between the internal limiting membrane and the external limiting membrane) and retinal pigment epithelium in superior, temporal, inferior and nasal sectors within 3 mm and 6 mm were calculated separately and automatically (Fig. 2). The automated central subfield thickness was defined as central retinal thickness. Within the 3-mm intermediate ring, the values in the superior, nasal, inferior and temporal zones were recorded for analysis. In the study group, only the measurements of the fellow eyes were used for comparison with the control group.

Sample size was determined at 80% power and 0.05 significance (95% confidence interval) level from

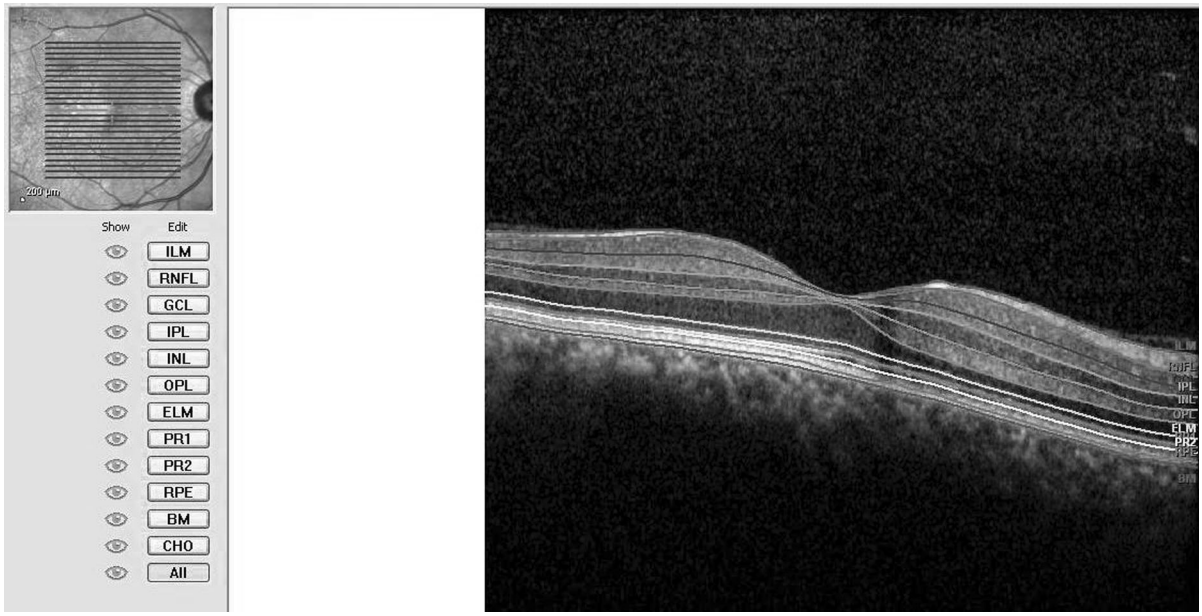

Fig. 1 Figure shows automatic segmentation of each retinal layer by spectral optical coherence tomography (Heidelberg Spectral Domain Optical Coherence Tomography; Heidelberg Engineering, Dossenheim, Germany). Segment lines show internal limiting membrane, retinal nerve fiber, ganglion cell, inner plexiform, inner nuclear, outer plexiform and outer nuclear layers, external limiting membrane, photoreceptors, retinal pigment epithelium and Bruch membrane

previous similar literature and was found to be 65 subjects per group. Statistical analysis was performed by SPSS statistical software (SPSS 11.0.0 for MS Windows; SPSS Inc., Chicago, IL). Kolmogorov–Smirnov test was used for determination of the distribution of the data. Parametric tests were used for comparison of homogenously distributed data, whereas nonparametric tests were used for comparison of non-homogenously distributed data. Categorical variables were compared with the Chi-square test. A $p < 0.05$ was considered significant.

Results

A total of 192 eyes of 192 participants were included in the study. The RVO group was consisted of 26 fellow eyes of 26 unilateral CRVO patients and 61 fellow eyes of 61 unilateral BRVO patients, whereas the control group comprised 105 eyes of 105 subjects without RVO. The mean age was 64.1 ± 9.3 years in the study group, whereas it was 63.3 ± 7.5 years in the control group ($p = 0.496$). Female/male ratio was 41/46 in the study group and 58/47 in the control group ($p = 0.263$).

In the study group, 49 (56.3%) patients had systemic hypertension (14 had CRVO and 35 had BRVO), 6 (6.9%) patients had cardiovascular disease (all had BRVO), and 26 (29.9%) patients had both systemic hypertension and cardiovascular disease (11 had CRVO and 15 had BRVO). One (1.1%, CRVO) patient had diabetes mellitus. The difference in systemic diseases was not significant in CRVO and BRVO groups ($p = 0.066$). In the control group, 34 (32.4%) patients had systemic hypertension and 3 (2.9%) patients had both systemic hypertension and cardiovascular disease.

The mean duration of RVO was 21.5 ± 12.4 months. Visual acuity and intraocular pressure levels were not significantly different in the study and the control groups (0.9 ± 0.1 vs. 0.8 ± 0.2 in the study and the control groups, respectively, in decimals; $p = 0.097$; 14.5 ± 2.8 mmHg vs. 14.8 ± 2.3 mmHg in the study and the control groups, respectively, $p = 0.579$).

The comparison of the macular layers between the study group and the control group was significant in only the inferior sector in 3-mm intermediate ring in the inner plexiform layer, with greater values in the control group ($p = 0.047$, Table 1). When a subgroup

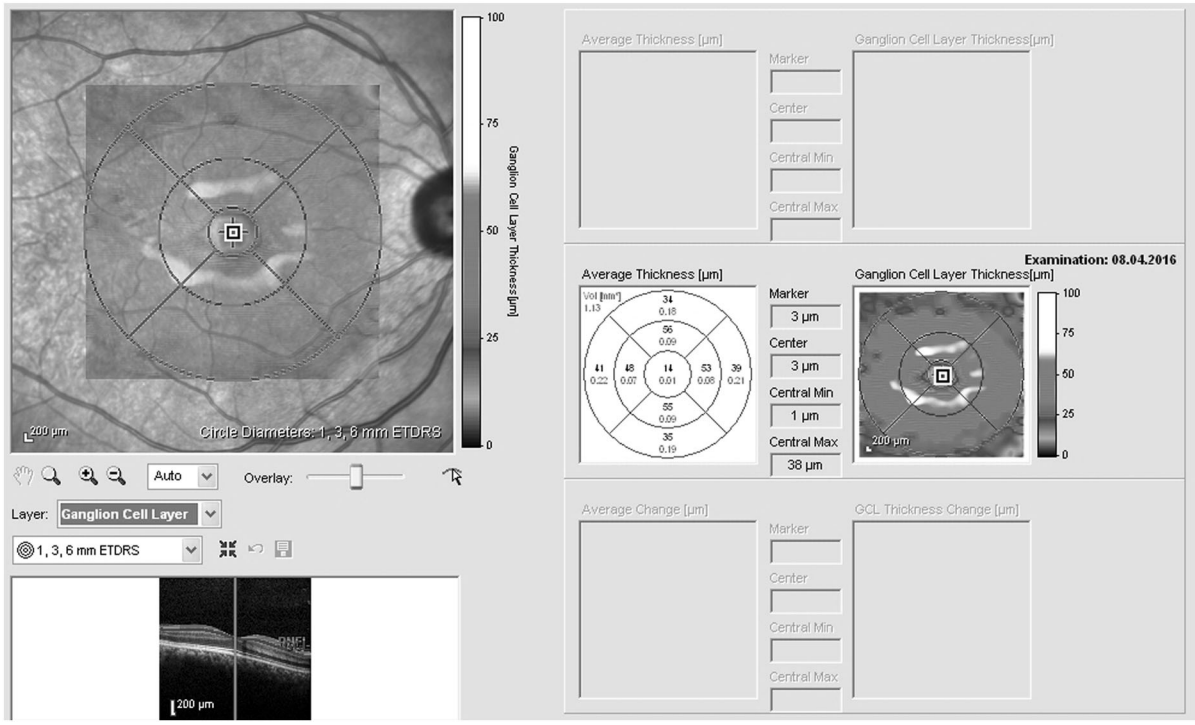

Fig. 2 By the segmentation application, the thicknesses of retinal nerve fiber layer, ganglion cell, inner plexiform, inner nuclear, outer plexiform, outer nuclear and photoreceptor layers, inner retina and retinal pigment epithelium in superior, temporal, inferior, nasal sectors within 3 mm and 6 mm can be calculated separately and automatically by SD-OCT. Figure shows the ganglion cell layer thickness in 4 sectors (superior, temporal, inferior and nasal) within 3 mm and 6 mm centered on the fovea

analysis was performed between the study group and the eyes of healthy subjects with no systemic diseases, the retinal thickness was significantly greater in the control eyes compared to the fellow eyes of RVO patients in the following layers/sectors: inferior retina; superior, inferior, nasal and temporal sectors in RNFL; superior and inferior sectors in ganglion cell layer; superior, inferior, temporal and nasal sectors in inner plexiform layer; superior and inferior sectors in inner retinal layers and central sector in RPE ($p < 0.05$).

When the fellow eyes of patients with CRVO were compared with the fellow eyes of the patients with BRVO, retinal thickness was lesser in the BRVO group compared to that in the CRVO group in the some sectors (central retinal thickness, central ganglion cell layer, central inner and outer plexiform layers and central inner retina; $p = 0.017$, $p = 0.001$, $p = 0.004$, $p = 0.010$ and $p = 0.008$, respectively).

Discussion

We found significant thinning in only the inferior sector in the inner plexiform layer in the fellow eyes of RVO patients compared with controls. When the study group was compared with the eyes of healthy subjects without any systemic diseases, the RNFL and the inner plexiform layers were the most affected layers which showed significant thinning in all quadrants. Inner retina was more likely to be affected compared to outer retina. Central macular thickness was lesser in the fellow eyes of patients with BRVO compared to that in CRVO.

Previous studies revealed that the fellow eyes of unilateral RVO patients have increased risk of developing RVO and show structural and electrophysiological changes compared with the general population [6–8]. In the study of Sakaue et al. [8] abnormal electroretinograms were reported in the fellow eyes of 36% of the patients with unilateral CRVO. In another study, the authors reported decreased sensitivity on

Table 1 Comparison of the thickness of retinal layers between the study and the control groups

	Study group $n = 87$	Control group $n = 105$	p value
Total retinal thickness (μm)			0.919
Central subfield (1 mm)	263.9 ± 20.8	263.6 ± 22.5	
Intermediate ring (3 mm)			
Superior[a]	338.1 ± 16.2	338.3 ± 21.6	0.337
Temporal	326.1 ± 17.5	326.5 ± 19.8	0.873
Inferior	332.9 ± 20.3	335.2 ± 20.5	0.457
Nasal	336.5 ± 15.7	337.0 ± 21.3	0.840
Retinal nerve fibers (μm)			0.961
Central subfield (1 mm)[a]	11.7 ± 2.1	11.6 ± 2.4	
Intermediate ring (3 mm)			
Superior	23.7 ± 2.8	24.4 ± 4.3	0.157
Temporal[a]	17.9 ± 1.8	18.6 ± 2.7	0.306
Inferior	23.6 ± 3.4	24.2 ± 3.8	0.291
Nasal[a]	20.1 ± 2.2	20.5 ± 3.2	0.349
Ganglion cell (μm)			0.593
Central subfield (1 mm)[a]	13.9 ± 3.6	14.0 ± 5.2	
Intermediate ring (3 mm)			
Superior[a]	51.3 ± 5.4	51.4 ± 7.8	0.345
Temporal	45.8 ± 6.6	46.3 ± 7.5	0.616
Inferior[a]	49.8 ± 6.7	50.6 ± 7.6	0.157
Nasal	49.1 ± 5.6	48.9 ± 7.9	0.805
Inner plexiform (μm)			0.897
Central subfield (1 mm)	19.7 ± 3.2	19.6 ± 3.6	
Intermediate ring (3 mm)			
Superior	40.1 ± 3.9	40.5 ± 5.0	0.544
Temporal[a]	39.4 ± 4.2	40.2 ± 4.6	0.087
Inferior[a]	38.9 ± 5.0	40.2 ± 4.9	**0.047**
Nasal[a]	40.4 ± 3.8	40.6 ± 4.8	0.475
Inner nuclear (μm)			0.299
Central subfield (1 mm)	19.8 ± 5.7	20.7 ± 5.8	
Intermediate ring (3 mm)			
Superior	41.8 ± 4.7	41.4 ± 4.3	0.567
Temporal	38.9 ± 4.5	38.8 ± 4.6	0.858
Inferior	40.7 ± 5.0	40.5 ± 4.3	0.772
Nasal	41.8 ± 4.5	42.2 ± 4.7	0.542
Outer plexiform (μm)			0.890
Central subfield (1 mm)[a]	24.3 ± 5.9	24.4 ± 6.3	
Intermediate ring (3 mm)			
Superior[a]	33.2 ± 6.9	33.2 ± 6.9	0.884
Temporal[a]	30.4 ± 5.1	29.5 ± 4.9	0.400
Inferior[a]	32.4 ± 7.3	32.1 ± 7.3	0.597
Nasal[a]	33.7 ± 7.3	34.8 ± 9.7	0.772
Outer nuclear (μm)			0.768
Central subfield (1 mm)	88.6 ± 13.4	89.2 ± 14.1	

Table 1 continued

	Study group $n = 87$	Control group $n = 105$	p value
Intermediate ring (3 mm)			
Superior	67.6 ± 8.7	67.0 ± 11.1	0.681
Temporal	71.2 ± 8.4	71.6 ± 8.9	0.746
Inferior[a]	67.1 ± 9.9	66.9 ± 10.8	0.970
Nasal	68.4 ± 10.7	66.9 ± 13.9	0.396
Retina pigment epithelium (μm)			0.120
Central subfield (1 mm)[a]	15.5 ± 1.8	15.9 ± 1.8	
Intermediate ring (3 mm)			
Superior[a]	15.2 ± 2.1	15.1 ± 2.0	0.637
Temporal[a]	14.3 ± 1.7	14.4 ± 1.6	0.708
Inferior[a]	14.6 ± 1.7	14.4 ± 1.6	0.256
Nasal[a]	14.9 ± 1.7	14.9 ± 1.7	0.623
Inner retina (μm)			0.854
Central subfield (1 mm)	178.8 ± 20.3	178.2 ± 21.8	
Intermediate ring (3 mm)			
Superior[a]	256.7 ± 15.3	257.0 ± 20.2	0.275
Temporal	244.2 ± 15.3	244.9 ± 18.0	0.775
Inferior[a]	252.7 ± 17.7	254.6 ± 20.0	0.381
Nasal	254.8 ± 16.2	255.4 ± 20.1	0.829
Photoreceptors (μm)			0.586
Central subfield (1 mm)	85.3 ± 3.9	85.7 ± 4.1	
Intermediate ring (3 mm)			
Superior	80.7 ± 3.3	80.4 ± 3.2	0.528
Temporal	80.6 ± 3.1	80.0 ± 3.2	0.209
Inferior	79.9 ± 3.0	79.3 ± 3.1	0.153
Nasal	81.5 ± 3.1	80.6 ± 3.4	0.062

Independent samples T test

[a]Mann–Whitney U test was used for non-homogenously distributed data

$p < 0.05$ was considered significant and printed in bold

microperimetry in the fellow eyes of RVO patients compared to normative data [10]. Kim et al. [7] compared peripapillary RNFL thickness in the fellow eyes of unilateral RVO patients with control subjects. They found that RNFL thickness was decreased especially in the inferior and superotemporal sectors in the fellow eyes compared to the controls. Glaucomatous visual field damage corresponding to RNFL defects was also documented in 19% of the fellow eyes, whereas it was documented in 2.8% of the control eyes. Pinhas et al. [10] analyzed inner retinal thickness/total retinal thickness ratio as assessed by SD-OCT in 10 fellow eyes of patients with CRVO. They found that inner retina was thinner in the fellow eyes compared to controls, but the difference was not statistically significant. In our study, only the inferior sector in 3-mm intermediate ring in the inner plexiform layer was thinner compared with controls. When the study group was compared with the eyes of healthy subjects without any systemic diseases, inner retina was significantly thinner in inferior and superior quadrants and particularly the RNFL and the inner plexiform layers in the fellow eyes of RVO patients. The difference in findings between the studies may be due to the difference in sample sizes (10 eyes in the former study vs. 87 eyes in our study).

Angiographic studies revealed a better understanding regarding the subclinical changes in the fellow eyes of RVO patients. Tsui et al. [9] found late vascular leakage on ultra-widefield fluorescein angiography in 10% of the fellow eyes of unilateral BRVO patients. Adaptive optics scanning light ophthalmoscope fluorescein angiography studies showed decreased foveal microvascular density and increased non-perfused capillaries in the fellow eyes of unilateral RVO patients compared with the controls [10]. Recently, Adhi et al. assessed perifoveolar retinal capillary network in RVO patients using SD-OCT angiography [11]. They enrolled 15 patients with unilateral CRVO and 8 patients with unilateral BRVO and 8 eyes of 8 age-matched healthy controls. They found decreased vascular perfusion in the fellow eyes in 53% of the patients with CRVO and 25% of the patients with BRVO at the deep plexus and in 20% of the patients with CRVO and none of the patients with BRVO at the level of the superficial plexus. Vessel tortuosity was seen in 60% and 25% of the fellow eyes of patients with CRVO and BRVO, respectively. No collaterals were noticed in the fellow eyes. Neither a decrease in perfusion, nor vascular tortuosity or collaterals was documented in the healthy control eyes. We hypothesized that the fellow eyes of RVO patients also have decreased perfusion despite that there is lack of clinically visible vascular occlusion findings and this might be the reason of the structural changes in the retina compared with the control group with no underlying systemic risk factors. However, more data are needed to reveal any association between the subclinical retinal structural changes and the vascular compromise preceding the vein occlusion.

Those changes in the fellow eyes may be related with general risk factors such as increasing age, hypertension, diabetes and arteriosclerosis, which may affect both eyes. Additionally, despite that the risk factors of RVO vary and there are certain differences in the pathogenesis of each risk factor, the subclinical inflammation with the production of reactive oxygen species may be a common shared step [10, 12–15]. Therefore, inflammation along with reactive oxygen species can cause epithelial damage leading to capillary closure even before the clinical findings become apparent. Furthermore, leukostasis which can be triggered by the increased expression of adhesion molecules during inflammation can contribute to vascular occlusion [10, 16].

Another finding in our study was that the central macular thickness was thinner in the fellow eyes of BRVO patients compared to the fellow eyes of CRVO patients. The thinning was more remarkable in the central inner retina. Based on the previous studies, capillary occlusion might explain the structural changes in the fellow eyes of RVO patients; however, there are very limited data comparing the retinal capillary network and perfusion in the fellow eyes of CRVO versus BRVO currently and these data suggested that vascular compromise was more prominent in the fellow eyes of CRVO than that in BRVO [10, 11]. Another possible explanation is that the reason of thinning may not be vascular, but rather neurodegenerative secondary to inflammatory events related to the underlying pathologies, which led to RVO eventually [12–15]. The factors, which make this pathway end up with CRVO or BRVO, are unclear. In our study, subclinical retinal thinning was more prominent in BRVO group; however, the groups were compatible in terms of comorbidities. Our finding needs to be confirmed with further studies comparing the fellow eyes of CRVO versus BRVO patients.

The main limitation of our study is its retrospective nature; therefore, some data, which may be related to retinal structural changes, such as smoking habits, the duration of systemic diseases or systemic medications, are missing.

In conclusion, an acute-on-chronic mechanism was suggested previously regarding RVO. In this mechanism, the chronic subclinical capillary non-perfusion causes local tissue hypoxia and release of reactive factors such as endothelin-1 and vascular endothelial growth factor, eventually clinical findings of RVO [10, 17]. Based on this suggestion, the subclinical changes in the fellow eyes may point out chronic findings preceding the acute "RVO" clinical findings. In our study, we found that the retinal thicknesses in the fellow eyes showed significant difference between the CRVO and BRVO patients. Additionally, inner plexiform layer showed sectoral thinning in the fellow eyes of unilateral RVO patients compared with the controls; however, the thinning was more prominent in the inner retinal layers, particularly in the RNFL and the inner plexiform, when the fellow eyes were compared with the eyes of healthy subjects without systemic risk factors. Those findings suggest that the

structural alterations found in the fellow eyes of unilateral RVO patients were associated with the underlying systemic vascular diseases. Further studies are needed to clarify whether those structural and functional changes in the fellow eyes make them vulnerable to further insults or may be a predictor of increased risk of future occlusion.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

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