Original Article

Optical coherence tomography angiography in intermediate uveitis-related cystoid macular edema

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ABSTRACT

Background: Cystoid macular edema (CME) is the leading cause of permanent visual impairment in patients with uveitis, particularly in patients with intermediate uveitis (IU). This study was aimed at comparing the changes in the macular microvasculature in patients with IU with uveitic non-responsive CME and without macular edema.

Methods: In this case-control study, 55 eyes of patients with IU were assessed for macular microvascular structures, including vascular density, foveal avascular zone (FAZ) measurement, and vascular morphological changes, using spectral-domain optical coherence tomography angiography (OCT-A) with the AngioVue OCT-A system. We divided patients into the following two groups: the case group, including 30 eyes with IU-related non-responsive CME, and the control group, including 25 eyes with IU without macular edema.

Results: Participants in the case and control groups had comparable age (P = 0.753) and sex (P = 0.124) distributions. Superficial capillary plexus vessel density in the case group was significantly decreased in the whole image (P = 0.027) and the parafoveal area (P = 0.001) compared to the control group. However, there were no statistically significant differences between the two groups in terms of foveal superficial vessel density, deep capillary plexus vessel density, FAZ area, FAZ perimeter, FAZ acircularity index, or foveal vessel density in a 300-μm-wide annulus around the FAZ (all P > 0.05). Vascular morphological changes, such as the capillary tuft, telangiectatic vessels, or micro-aneurism, were not different in the overview images of the OCT-A printout between the two groups.

Conclusions: The mean superficial capillary plexus vessel density was lower in eyes with IU-related nonresponsive CME than in those without macular edema. We observed more cystoid spaces in SCP than in DCP. Microcystic changes in the inner retina and ischemia may be the underlying cause in eyes with nonresponsive CME. Future prospective longitudinal studies with healthy, matched controls are warranted to confirm our findings.

KEY WORDS

optical coherence tomography, angiography, intermediate uveitis, cystoid macular edema, macular microvasculature, macular edema, fovea centralis

INTRODUCTION

The frequency of cystoid macular edema (CME) varies in different uveitis entities, ranging from 66% in patients with panuveitis to 11% in those with anterior uveitis. It is a leading cause of permanent visual impairment in approximately 40–50% of patients with uveitis [1] and the most frequent cause of visual impairment in patients with intermediate uveitis (IU) [2-4]. Patients with IU and associated systemic diseases are less likely to exhibit macular edema [5].

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However, the exact pathophysiology of uveitic CME remains unclear [6]. The integrity of the blood-retinal barrier safeguards the ocular neurons and photoreceptors. Various inflammatory mediators, such as prostaglandins, interleukins, interferon-gamma, and tumor necrosis factor-α, induce the breakdown of the blood-retinal barrier, leading to fluid outflow into and under the retinal layers, resulting in extracellular edema [7, 8]. Müller glial cell swelling is another proposed cause of CME. Intracellular fluid accumulation in the absence of vascular leakage results in cystic space formation by swollen and dying Müller cells [9, 10].

Spectral-domain optical coherence tomography angiography (SD-OCTA) is a new imaging modality that uses advances in the OCT technology. This results in a high-resolution angiographic display of the retinal microvascular structure. It detects variations in the intensity and phase properties of the OCT signal over multiple B-scans resulting from red blood cell movements [11-13]. It allows the qualitative and quantitative evaluation of the microvascular integrity in retinal vascular diseases, primarily in the parafoveal area, where visually significant pathology is present. In addition, SD-OCTA provides high-resolution macular capillary structural details along with a quantitative assessment of disease severity. OCT-A enables clinicians to evaluate the parafoveal capillary characteristics and changes in patients with old macular edema. The invasive imaging technique fluorescein angiography (FA) is the gold standard, but leakage from abnormal vessels prevents capillary-level resolution. SD-OCTA is a non-invasive method that provides near-histology-level resolution to assess capillary density [12, 14].

This study aimed to evaluate and compare the perifoveal microvascular changes in patients with known IU, with or without CME, using SD-OCTA (AngioVue).

METHODS

This single-center, case-control study was conducted between March 2017 and February 2018. The study followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the Tabriz University of Medical Sciences, Tabriz, Iran. Written informed consent was obtained from eligible participants, and patient confidentiality was safeguarded throughout the study.

Thirty-seven patients with known IU, with or without CME, were recruited consecutively from the outpatient department of the Nikoukari Eye Hospital. The diagnosis of IU was based on the diagnostic criteria laid down by the Standardization criteria in Uveitis Nomenclature (SUN working group) and the National Eye Institute system [15, 16]. In this study, cases of IU with apparent control of inflammation, no white blood cells in the anterior chamber or vitreous, and CME persistent for over 6 months despite conventional immunosuppressive treatments were considered to be non-responsive CME.

Patients with ocular comorbidities other than IU, significant media opacities, non-inflammatory or pseudophakic CME, a history of diabetes mellitus or eye surgery, inability to keep the head or eye fixed, or low image quality, and pregnant or lactating women were excluded.

Eligible participants underwent complete history-taking and detailed ocular examination, including measurement of best-corrected distance visual acuity using a Snellen chart (auto chart projector CP 670; Nidek Co., Ltd, Gamagori, Japan), slit-lamp examination (Haag-Streit BM 900 slit lamp, Haag-Streit Diagnostics, Bern, Switzerland), intraocular pressure measurement using applanation tonometry (Goldmann, AT 900 C/M; Haag-Streit, Bern, Switzerland), and dilated fundus examination using a +78 D lens (VOLK Optical, Mentor, OH, USA).

All participants underwent imaging with the SD-OCTA AngioVue Imaging System (Optovue, Inc., Freemont, CA, USA) using the split-spectrum amplitude-decorrelation angiography (SSADA) algorithm to refine the signal-to-noise ratio [17, 18]. The A-scan rate of this instrument (AngioVue) is 70,000 scans/s, with a light source centered at 840 nm. Each OCT-A volume contained 304 × 304 A-scans, with two consecutive B-scans captured at each fixed position [19, 20]. Each OCT-A volume was taken in 3 s, and two orthogonal OCT-A volumes were acquired for orthogonal registration using motion correction technology to minimize motion artifacts [19-22]. Poor-quality OCT-A images, such as with signal loss due to fixation loss or blinking, a low-quality score, motion or projection artifacts, shadowing or blurring in en face, or inaccurate segmentation of tissue layers, were excluded.

The 6 × 6 foveal centered OCT-A and foveal (1.5 × 1.5 mm) and parafoveal areas' (0.5 mm diameter) horizontal maps were evaluated for the following parameters: macular thickness; intraretinal cystoid spaces; perifoveal anastomotic capillary morphological changes, such as the capillary tuft, telangiectatic vessels, or micro-aneurism; and areas of capillary nonperfusion or hypoperfusion (presenting as central irregular hypointense areas). Quantitative analysis of OCT angiograms included foveal avascular zone (FAZ) area and capillary vessel density (VD) measurements (SSADA extracted the OCT-A information).

We used AngioAnalytics (RTVue-XR version: 2017.1.0.151) flow density map software, which is a quantification tool for the vessel area density and non-flow area to measure FAZ. Using VD mapping, we evaluated the relative flow density in the superficial and deep retinal layers as a percentage of the total measured area. The superficial capillary plexus (SCP) is segmented from the internal limiting membrane to the inner plexiform layer, while the deep capillary plexus (DCP) is segmented from the inner nuclear layer to the outer plexiform layer. The FAZ area was measured in mm^2 using the non-flow function in the OCT-A software and automatically calculated by the AngioAnalytics software [23-25].

Statistical analyses were performed using SPSS 20.00 for Windows (IBM Corp., Armonk, N.Y., USA). Normality was assessed using the Kolmogorov–Smirnov test. The independent-samples *t*-test was used to compare quantitative data, and the chi-square test was used for qualitative data. Descriptive statistics were expressed as frequency (%) for categorical variables and mean ± standard deviation for normally distributed variables. Statistical significance was set at $P < 0.05$.

RESULTS

We enrolled 55 eyes of 37 patients with known IU, including 30 eyes of 20 patients with non-responsive CME (case group) and 25 eyes of 17 patients without macular edema (control group). All participants had clinically inactive inflammation, phakic eyes, and no history of ocular surgery. Patients in the control group had no history of macular edema.

The case and control groups were comparable in the patient age ($P = 0.753$) and sex ($P = 0.124$) distributions. The most common underlying cause of IU was idiopathic in both groups (90% in the case group and 88% in the control group; Table 1). The duration of uveitis or associated systemic disease did not differ significantly between the two groups ($P = 0.940$ and $P = 0.880$, respectively; Table 1).

Reviewing the medical records of our patients revealed that prior and concomitant treatment regimens of non-infectious IU included the use of topical corticosteroids, oral non-steroid anti-inflammatory drugs, regional steroid injections (trans-septal, sub-Tenon, or intravitreal triamcinolone acetonide injections), systemic steroids, and immunosuppressants (anti-metabolites or biologic response modifier drugs) as steroid-sparing agents. Biologic response modifier agents were not administered for multiple sclerosis-associated IU. Pan-retinal photocoagulation was applied to peripheral neovascularization associated with IU when indicated. The treatment options were more aggressive for IU with CME. Infectious IU was treated based on a pathologic microbial agent causing tuberculosis and treated with the standard 6-month anti-tuberculosis drug regimen. Topical and regional steroids were administered when inflammation was not adequately controlled.

The vascular structure of the whole image in the 6 × 6-mm scan and the foveal (1.5 × 1.5 mm) and parafoveal (0.5-mm diameter) areas were analyzed in both groups using superficial and deep layer vascular information. The mean SCP VD decreased significantly in the whole image and parafoveal area in non-responsive CME eyes compared to control eyes ($P = 0.027$ and $P = 0.001$, respectively). Likewise, this parameter numerically decreased in the foveal area in the case group, although without a statistically significant difference from the control group ($P = 0.711$; Figure 1, Table 2).

Table 1. Characteristics of study groups

Variables	Case group (n = 30 eyes)	Control group (n = 25 eyes)	*P*-value
Age (y), Mean ± SD (Range)	38.2 ± 7.9 (16 to 58)	40.3 ± 9.4 (21 to 59)	0.753
Sex (Male/Female), n of patients (%)	8 (40) / 12 (60)	7 (41.2) / 10 (58.8)	0.124
Cause of IU, n of eyes (%)	Idiopathic: 27 (90) MS: 2 (6.7) TB: 1 (3.3)	Idiopathic: 22 (88) RA related uveitis: 1 (4) Sarcoidosis: 1 (4) TB: 1 (4)	-
Duration of CME (m), Mean ± SD (Range)	7.6 ± 2.2 (6 to 13)	-	-
Time interval between diagnosis of IU and manifestation of CME (m), Mean ± SD (Range)	19.7 ± 19.0 (1 to 60)	-	-
Duration of IU (m), Mean ± SD (Range)	23.7 ± 16.3 (7 to 72)	24.6 ± 16.2 (8 to 70)	0.940
Duration of systemic disease (m), Mean ± SD (Range)	30.4 ± 18.7 (12 to 80)	30.2 ± 18.5 (10 to 78)	0.880

Abbreviations: n, number; y, years; SD, standard deviation; %, percentage; IU, intermediate uveitis; MS, multiple sclerosis; TB, Tuberculosis; RA, rheumatoid arthritis; CME, cystoid macular edema; m, months. Note: The duration of uveitis was calculated from the onset of uveitis, and the duration of systemic disease was from the initiation of diagnosis of systemic disease; Case group, eyes with IU-related nonresponsive cystoid macular edema; Control group, eyes with IU without macular edema.

Table 2. Optical coherence tomography angiography parameters of the macula in study groups

Parameter	Case Group Mean ± SD	Control Group Mean ± SD	*P*-value
Superficial VD (Whole image) (%)	41.92 ± 5.37	45.78 ± 5.56	**0.027**
Superficial VD (Foveal) (%)	17.09 ± 8.28	17.94 ± 6.72	0.711
Superficial VD (Parafoveal) (%)	39.03 ± 9.75	47.48 ± 6.75	**0.001**
Deep VD (Whole image) (%)	44.78 ± 6.40	45.03 ± 7.24	0.906
Deep VD (Foveal) (%)	32.94 ± 11.81	33.04 ± 8.06	0.973
Deep VD (Parafoveal) (%)	49.95 ± 6.44	51.82 ± 6.92	0.369
Whole thicknesses (µm)	334.50 ± 30.89	308.58 ± 27.38	**0.005**
Parafoveal thickness (µm)	381.89 ± 46.70	331.38 ± 31.51	**< 0.001**
Central foveal thickness (µm)	356.17 ± 137.98	256.19 ± 35.67	**0.001**
FAZ area (mm²)	0.34 ± 0.22	0.31 ± 0.10	0.586
Perimeter of FAZ (mm)	2.21 ± 0.86	2.17 ± 0.42	0.851
Acircularity index of FAZ	1.14 ± 0.05	1.12 ± 0.05	0.104
Foveal VD in a 300-µm wide annulus*(%)	40.79 ± 11.04	45.10 ± 10.16	0.202

Abbreviations: SD, standard deviation; VD, vessel density; %, percentage; µm, micrometer; FAZ, foveal avascular zone; mm², square millimeters. *A concentric ring with an inner border at the FAZ margin and outer border at 300-µm away from the FAZ margin [33]. Note: Case group, 30 eyes with intermediate uveitis-related nonresponsive cystoid macular edema; Control group, 25 eyes with intermediate uveitis without macular edema. *P*-value < 0.05 is shown in bold.

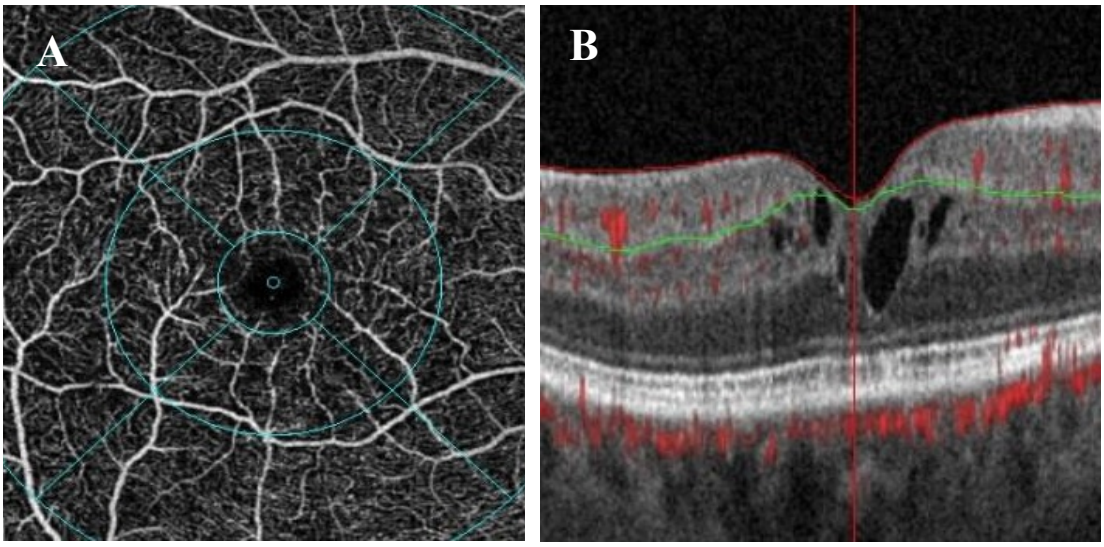

Figure 1. (A) En-face optical coherence tomography (OCT) angiogram segmented at the level of the superficial retinal capillary plexus from the right eye of a patient in case group with nonresponsive intermediate uveitis-related cystoid macular edema. (B) OCT B-scan shows a moderate retinal thickening with intraretinal cystoid spaces in the inner retina layers.

The mean DCP VD in the whole image and foveal and parafoveal areas were slightly lower in eyes with nonresponsive CME, although without a statistically significant difference from the control group (all $P > 0.05$; Table 2). There were no significant differences between the two groups in the FAZ area or perimeter, acircularity index, or foveal VD in the 300-µm-wide annulus around FAZ (all $P > 0.05$; Table 2). The whole image thickness of the macula ($P = 0.005$), parafoveal thickness ($P < 0.001$), and central foveal thickness ($P = 0.001$) were significantly greater in the case group than in the control group (Table 2).

In the case group, cystoid spaces were observed in the SCP of all 30 eyes (100.0%) and DCP of 20 eyes (66.7%). We found no differences in vascular morphological changes, such as the capillary tuft, telangiectatic vessels, or micro-aneurism, in the overview images of the OCTA printout between the two groups.

DISCUSSION

In the current study, age and sex distributions as well as the duration of uveitis and associated systemic disease were comparable between the case and control groups. We found a significant decrease in SCP VD in both the whole image and the parafoveal area in patients with IU and non-responsive CME compared to the control group. However, the foveal SCP, DCP, and FAZ areas, FAZ perimeter, FAZ acircularity index, and foveal VD in a 300-μm-wide annulus around FAZ were comparable. No difference was noted in the vascular morphological changes in the overview images between the two groups.

The superiority or equivalence of OCT-A over FA in delineating the retinal vasculature has been verified in healthy and diseased eyes [11, 13, 26-28]. However, Kim et al. found discrepancies in FA and OCT-A findings in the diagnosis of macular edema in 44% of the eyes with idiopathic IU, and treatment responses varied according to the discrepant pattern [29]. The discrepancy found in 46% of the eyes with various subtypes of uveitis complicated by macular edema is more common in young patients with IU [30]. These findings may indicate that FA and OCT-A are complementary investigations, each disclosing distinct aspects of the uveitic macular edema pathophysiology. The current study assessed parafoveal microvascular changes in patients with nonresponsive IU-related CME using the novel noninvasive high-quality imaging technique SD-OCTA. Previously, we used FA for this purpose, but the parafoveal vascular anatomy was obscured because of leakage from abnormal blood vessels.

A few studies have examined microvascular changes in patients with IU in the presence of CME. In a prospective, cross-sectional study using swept-source OCT-A, Tian et al. [31] included 93 eyes of 58 adult patients with a mean age of 45.9 years and clinically inactive noninfectious IU with/without retinal vasculitis, with most cases being idiopathic (63%). Thirty-four eyes of 17 healthy, age-matched participants with a mean age of 42 years were included in the control group. The single wide-field montage 12 × 12-mm scan and 3 × 3-mm OCT angiograms of all included eyes were reviewed. IU-mediated CME was observed in 18% of the eyes. The mean VD of the SCP was significantly lower in eyes with IU and vasculitis than in those with IU only and healthy controls. Eyes with IU and vasculitis had a higher prevalence of non-perfusion in both SCP and DCP on wide-field montage scans but not in the 3 × 3-mm scans. The presence of CME was significantly associated with capillary non-perfusion and reduced perfusion in SCP and DCP of the 3 × 3-mm scans. The FAZ size, circularity, and raw length were significantly smaller in patients with IU only than in those with IU and vasculitis, as well as, healthy controls. Multivariable regression revealed that the presence of CME instead of the disease entity affected VD in SCP [31]. Likewise, in the current study, the SCP VD in the parafoveal area and the whole image was significantly lower in eyes with non-responsive IU-related CME than in eyes without CME. However, we found no significant differences in the FAZ area or perimeter, acircularity index, or foveal VD in the 300-μm-wide annulus around FAZ between eyes with and without CME among patients with clinically inactive IU. We included eyes with IU with or without CME; therefore, vitreous inflammation in these patients may have caused secondary subclinical ischemia [32] of the inner retina and subsequent alteration of VD in SCP relative to DCP.

Kim et al. [14] recruited patients with anterior, posterior, or panuveitis uveitis and healthy participants who underwent 3 × 3-mm^2 SD-OCTA scans centered on the fovea, with similar segmentation for SCP and DCP as in the current study. Overall, uveitic eyes revealed significantly lower VD parameters in both the superficial and deep retinal layers and the whole retina than in healthy eyes. When uveitic eyes with macular edema were compared to healthy eyes, a significantly lower VD in the deep retinal layer was noted, without further differences in SCP. Significant alterations in DCP were co-localized with intraretinal cystoid spaces, typically in the inner nuclear and plexiform layers [14]. Although patients with diabetes were included, the significance of the association between uveitis and healthy eyes remained constant after excluding eyes with concomitant diabetes from the study cohort. The OCT-A parameters were similar across all subgroups of uveitis compared to healthy eyes [14]. The findings of this study contradicted the findings of Kim et al., owing to the significant decrease in SCP VD in both the whole image and the parafoveal area in eyes with non-responsive IU-related CME compared to eyes with IU without CME. However, there are a few differences between these two studies, which limit their comparison. First, we included patients with IU with or without CME, while in their study, IU was not included in the analysis because of the lack of data. Second, in our study, the OCT-A parameters in eyes with IU and macular edema were compared to those of the same subtype of uveitis, whereas in their study, they were compared with those of healthy eyes. Third, different scanning areas were used in these studies, and a difference in VD results is observed by changing the size of the scanning area [33]. However, both studies showed a decrease in VD in uveitic eyes with macular edema. Kim et al. proposed the mechanical displacement theory as a possible cause of reduced VD [14], indicating that the findings of both studies should be interpreted with caution.

In a prospective, observational, comparative study by Khotchali et al. [27], 3 × 3-mm OCT angiograms in uveitis CME revealed cystoid space in DCP more than in SCP and VD changes in DCP more than in SCP. They included all types of uveitis with the IU subtype accounting for 66.7% of the cases (the most frequent underlying cause being idiopathic [53.1%]). Regarding CME chronicity, 52.8% of the eyes had macular edema for up to 6 months and 47.2% for over 6 months. They confirmed the superiority of swept-source OCT-A over FA in detecting and characterizing qualitative and quantitative retinal microvascular changes, which led to better assessment and comparison of involvement in SCP and DCP. In uveitic eyes with CME, black cystoid spaces were seen in DCP of all eyes and SCP in 16.7% of the eyes. Intraretinal cystoid spaces and capillary non-perfusion/hypoperfusion areas were more frequently observed in DCP than in SCP. The FAZ area in SCP in eyes with uveitic CME was comparable to that in the healthy control eyes. However, in the DCP, it was significantly larger in eyes with uveitic CME than in healthy control eyes. The capillary VD in the SCP and DCP was significantly lower in eyes with uveitic CME than in healthy control eyes. Eyes with macular edema for over 6 months showed a marked decrease in capillary VD and had a larger FAZ area in DCP than eyes with macular edema for up to 6 months, which may be due to the chronicity of the disease. On the final OCT-A examination of uveitic eyes after CME resolution, a larger FAZ area and/or lower capillary VD in DCP revealed a significant association with poor final visual acuity [27]. The exclusion criteria were similar to those used in this study, and the most common underlying cause of IU was idiopathic, as in the current study (90% in the case group and 88% in the control group). However, the mean duration of uveitis was longer (28 months, ranging from 15 days to 10 years) than the current study (case group: 23.7 months, ranging from 7 to 72 months; control group: 24.6 months, ranging from 8 to 70 months). Contrary to their findings, we found more cystoid spaces in SCP than in DCP (seen in SCP of all eyes and DCP of 66.7% of the eyes with nonresponsive uveitic CME). Furthermore, in our study, eyes with non-responsive CME for over 6 months had comparable FAZ area and perimeter, FAZ acircularity index, and foveal VD in a 300-μm-wide annulus around FAZ against eyes with IU without CME. We observed microvascular changes in the superficial layers rather than in the deep layers. These differences may arise from differences in the comparison groups between the two studies, the nonhomogeneous nature of the anatomical type of uveitis in Khotchali et al.'s study [27], postprocessing of the images, or other unknown factors. Since quantitative parameters, such as VD, are difficult to compare across devices, comparing the findings of numerous studies could be demanding and inconclusive. Furthermore, the presence of CME may vary because of inaccurate layer segmentation and displacement of capillaries by cystic spaces, which causes a lower VD per unit area [31].

This study provided useful OCT-A data as the reference value for diagnosing IU-related CME in patients with clinically inactive inflammation. The limitations of this study are the lack of choroidal microvascular data, including patients with a specific uveitis entity, and the absence of healthy control eyes. Further studies with healthy matched controls are warranted to confirm our findings. In addition, future studies of all subtypes of uveitis with clinically active and inactive inflammation are necessary to determine the exact macular vascular changes in nonresponsive uveitis-related CME. Longitudinal studies following a larger cohort with IU before, during, and after the development of CME using OCT-A could provide robust evidence for this entity. These studies could provide useful clinical data for the follow-up of patients with uveitic CME under treatment. Moreover, we did not assess the repeatability or reproducibility of qualitative or quantitative analyses. Further studies are required to address this limitation. We propose that the SUN working group set forward guidelines for homogenous segmentation and image post-processing in uveitis-related studies using OCT-A. Therefore, future studies evaluating the impact of uveitic CME on vessels and perfusion density are comparable.

CONCLUSIONS

IU-related nonresponsive CME was associated with microvascular changes observed as a decrease in VD of SCP in the parafoveal area and the whole image of the macula. We observed more cystoid spaces in SCP than in DCP. Microcystic changes in the inner retina and ischemia may be the underlying causes of these alterations in VD in SCP, which should be verified in a longitudinal follow-up study on uveitic CME under treatment.

ETHICAL DECLARATIONS

Ethical approval: The study followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the Tabriz University of Medical Sciences, Tabriz, Iran. Written informed consent was obtained from eligible participants, and patient confidentiality was safeguarded throughout the study.
Conflict of interest: None.

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