

Changes in Choroidal Vascularity Index (CVI) in Intermediate Uveitis

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Purpose: To investigate the longitudinal changes in choroidal vascularity index (CVI) in eyes with active and quiescent intermediate uveitis using enhanced depth imaging optical coherence tomography (EDI-OCT).

Methods: EDI-OCT images of eyes with active and quiescent intermediate uveitis were retrospectively reviewed and binarized using ImageJ software. Choroidal parameters including CVI, total choroidal area (TCA), luminal area (LA), stromal area (SA), and subfoveal choroidal thickness (SCT) were measured and compared between baseline and follow-up visits among eyes with active and quiescent intermediate uveitis.

Results: Thirty-eight eyes from 21 patients with active intermediate uveitis and 30 eyes from 17 patients with quiescent intermediate uveitis were included. CVI in eyes with active intermediate uveitis significantly increased from baseline ($66.50\% \pm 3.40\%$) with resolution of inflammation on follow-up ($68.82\% \pm 3.90\%$; $P < 0.001$). In eyes with quiescent intermediate uveitis at baseline eyes, CVI did not significantly change after follow-up ($66.34\% \pm 3.19\%$ to $66.25\% \pm 3.13\%$; $P = 0.850$).

Conclusions: CVI significantly increased when active inflammation in intermediate uveitis resolved while CVI remained unchanged at follow-up in quiescent intermediate uveitis.

Translational Relevance: CVI may be a useful noninvasive tool to monitor treatment response in intermediate uveitis. Our findings also highlight the involvement of choroidal vasculature in uveitic eyes without any clinical evidence of choroiditis.

Introduction

Intermediate uveitis (IU), which consists of inflammation of the vitreous cavity and peripheral retina, has an estimated incidence of 1.4–2.0 in 100,000.^{1–3} The cause of IU in the majority of cases is idiopathic.⁴ IU patients can develop sight-threatening complications that include cystoid macular edema, retinal vasculitis, and glaucoma.⁵ Therefore monitoring disease activity and identifying complications is important for preventing irreversible vision loss.

The development of enhanced depth imaging optical coherence tomography (EDI-OCT) has enabled

a noninvasive and more detailed assessment of the choroid. Choroidal vascularity index (CVI) is a novel imaging marker that can be obtained by using binarization techniques on EDI-OCT images.⁶ CVI allows quantitative evaluation of both choroidal vascular and stromal compartments. Several studies have shown that CVI is a useful OCT marker in different intraocular inflammatory conditions primarily in posterior uveitis diseases.^{7–11}

Previous studies have suggested choroidal involvement in IU but the extent of choroidal involvement in IU remains unclear.^{12–14} Histopathologic studies of pars planitis eyes have demonstrated inflammatory infiltration of the choroidal stroma.¹² More recently,

alteration of perfusion in the level of choriocapillaris in IU has been revealed using swept-source OCT angiography.^{13,14} However, no study to the best of our knowledge has quantitatively assessed longitudinal choroidal changes in IU using CVI.

Understanding the change in choroidal vascularity using a clinical imaging tool can potentially provide important insight into the pathophysiology and treatment response of IU. Thus, in this study, we aimed to evaluate longitudinal choroidal vascular changes in eyes with active and quiescent IU using CVI.

Methods

A retrospective review of EDI-OCT images from patients with a diagnosis of IU evaluated at the National Eye Institute from January 2017 to May 2021 was performed. The study was approved by the institutional review board of the National Institute of Health and the study performed in accordance with the tenets of the Declaration of Helsinki.

All patients were diagnosed with IU based on the standardization of uveitis nomenclature working group classification.³ Vitreous cell and vitreous haze grading scales were used as previously described.^{15,16}

Eyes with IU were classified into two groups according to clinical activity at baseline. Eyes were regarded as clinically active if they had one or more of the following: new-onset vitreous cells or vitreous haze, presence of retinal vascular leakage, or disc leakage on fundus fluorescein angiography (FFA). Eyes were clinically quiet if they were without any evidence suggestive of active inflammation (clinical findings or FFA).

In the active IU group, eyes were clinically active at baseline and clinically quiet at follow-up. “Follow-up” in this group was the first subsequent clinically quiet encounter. In the quiescent IU group, eyes were clinically quiet at baseline and at follow-up, which was the next chronological visit.

The exclusion criteria were as follows: (1) poorly defined choroidal-scleral junction (2) high myopia (refractive error > -6 diopters), (3) ocular surgery within one year at the time of examination, (4) coexistence of other macular or retinal diseases such as central serous chorioretinopathy, age-related macular degeneration, retinal vascular occlusion, or (5) history of systemic diseases such as diabetes, hypertension, cardiovascular disease, or previous history of ocular trauma.

Both eyes with intermediate uveitis of a patient were included if eligible. Patient data including demograph-

ics, refractive error, slit lamp biomicroscopy, intraocular pressure (IOP) measured by applanation tonometry (Tono-Pen; Reichert Technologies, Inc., Buffalo, NY, USA), FFA findings, disease activity, onset of IU, and complications related to IU were reviewed.

Image Acquisition

EDI-OCT images were obtained using the Spectralis OCT device (Heidelberg Engineering, Heidelberg, Germany). For each eye, two images were obtained: the first one at baseline and the second one at follow-up. Single horizontal subfoveal images were imported into ImageJ 1.51 software (National Institutes of Health, Bethesda, MD, USA) for analysis.

Image Analysis

A modification of a previously described method was used to calculate CVI.¹⁰ The EDI-OCT image was opened in ImageJ and the line tool was used to place a perpendicular line overlay through the center of the fovea. Two 750 μm lines were drawn from the center of the fovea to the nasal and temporal side with a total length of 1500 μm . The choroidal area encompassed under this line was the total choroidal area (TCA). Three vertices of the polygon were placed on both the upper border and lower border of the TCA. The upper border of the TCA was traced along the lower edge of retinal pigment epithelium (RPE), and the lower border of the TCA was traced along the choroid-scleral junction (Fig. 1B). The subfoveal choroidal thickness (SCT) measurement was performed on the original EDI-OCT images. SCT was measured perpendicular to the RPE, from the lower edge of RPE to the choroid-scleral junction at the fovea using the line tool in ImageJ.

To binarize the images, the EDI-OCT image was first converted to a 8-bit format then thresholded using Niblack's thresholding technique¹⁷ (Fig. 1C). The image was then converted back to a red, green, blue image. Next, the color threshold tool was used to demarcate the black pixels, representing the luminal (vascular) area (LA), and the white pixels, representing the stromal area (SA) (Fig. 1D). SA was obtained by calculating the differences between TCA and LA. Finally, CVI was calculated as a proportion of LA to TCA.

Choroidal parameters including, CVI, TCA, LA, SA and SCT, from EDI-OCT images were compared at baseline and follow-up in each group and between groups. The analysis of choroidal parameters was performed at the eye-level. All EDI-OCT images were

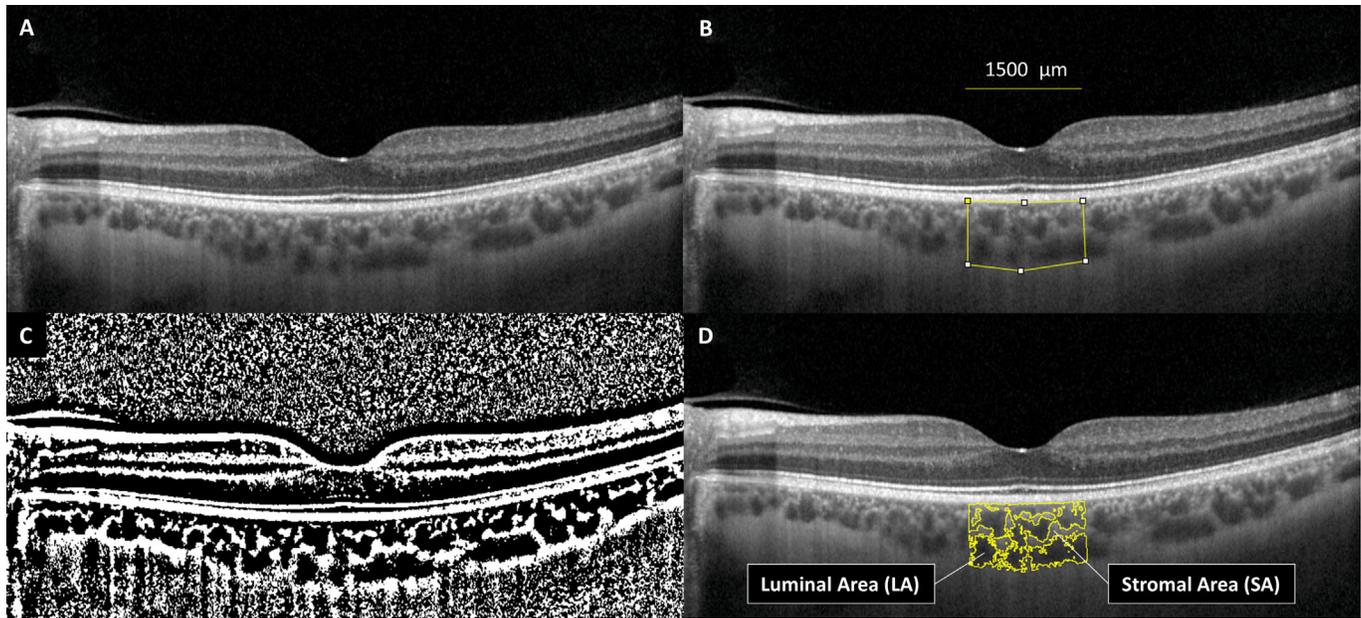


Figure 1. CVI calculation in a patient with acute intermediate uveitis. (A) Original EDI-OCT image. (B) The TCA is outlined using the polygonal selection tool within a width of 1500 μm (750 μm either side of the fovea). (C) Figure after image binarization with Niblack's autocal threshold tool. (D) Overlay of binarized image to the original EDI-OCT showing segmentation of choroidal structures. Light area represents SA and dark area represents LA. CVI was calculated dividing LA by TCA.

deidentified before being evaluated by two independent graders (W.K., A.K.). Their measurements were then averaged for statistical analysis.

Statistical Analyses

Data were expressed as the mean standard deviation for quantitative variables and as counts and percentages for categorical variables. The Shapiro-Wilk test was used to evaluate the normality of the data. Variables at baseline and follow-up in each IU group were compared using a paired *t*-test. At baseline, The Mann-Whitney *U* test or the unpaired *t*-test were used to compare quantitative variables between two groups, depending on the normality of the data. Categorical variables were analyzed using the χ^2 or Fisher's exact test. At follow-up, variables were adjusted with covariates using analysis of covariance and the adjusted variables were compared between the two groups. Intraclass correlation coefficient (ICC) was calculated to determine intra-eye correlation. The interobserver reliability of CVI and SCT calculation was assessed by measuring the ICC. All tests were two-sided, and $P < 0.05$ was considered significant. Statistical analysis was performed using SPSS 22.0 software (SPSS Inc., Chicago, IL, USA).

Results

Demographic and Clinical Characteristics

Demographic and clinical characteristics are summarized in [Table 1](#). Our study included 38 eyes from 21 patients from the active IU group (mean age, 32 ± 16.3 years; male/female, 9/12), and 30 eyes from 17 patients from the quiescent IU group (mean age 35 ± 20.4 years; male/female, 7/10). No significant difference was noted between active and quiescent IU groups in terms of age, gender, laterality, best-corrected visual acuity (LogMAR), refractive error, and IOP.

The mean disease duration was significantly shorter in the active IU group (1.29 ± 2.49 years) compared with quiescent IU group (6.11 ± 3.97 years; $P < 0.001$). The mean follow-up period in the active IU (3.81 ± 2.42 months) was significantly shorter compared to quiescent IU group (7.88 ± 4.27 months; $P < 0.001$).

Idiopathic IU was the most frequent cause in both active IU (81%) and quiescent IU (94%) groups. In the active IU group, complications during active inflammation included retinal vasculitis (33 eyes [87%]), cystoid macular edema (11 eyes [29%]), ocular hypertension (three eyes [8%]) and glaucoma (four eyes [11%]). Glaucoma was the only complication observed in the quiescent IU group (two eyes [7%]).

Table 1. Demographic and Clinical Characteristics in Intermediate Uveitis Patients

Characteristics	Active Group	Quiescent Group	P Value
Number of patients (eyes)	21 (38)	17 (30)	N/A
Age (y), mean \pm SD	32 \pm 16.3	35 \pm 20.4	0.43
Female	12 (57%)	10 (59%)	0.89
Bilateral	17 (81%)	13 (77%)	0.73
Best-corrected visual acuity (logMAR), mean \pm SD	0.14 \pm 0.26	0.17 \pm 0.34	0.64
Refractive error (diopters), mean \pm SD	-2.32 \pm 1.81	-2.78 \pm 3.57	0.53
IOP (mmHg), mean \pm SD	16.1 \pm 5.7	15.0 \pm 2.9	0.77
Vitreous cell grade, n eyes (%)			<0.001
0	0 (0)	20 (67)	
0.5+	15 (39)	6 (20)	
1+	20 (53)	3 (10)	
2+	3 (8)	1 (3)	
Vitreous haze grade, n eyes (%)			0.001
0	13 (34)	24 (80)	
0.5+	17 (45)	6 (20)	
1+	7 (18)	0 (0)	
2+	1 (3)	0 (0)	
Disease duration (years), mean \pm SD (range)	1.29 \pm 2.49 (0.08–6)	6.11 \pm 3.97 (1–13)	<0.001
Follow-up period (months), mean \pm SD (range)	3.81 \pm 2.42 (2–10)	7.88 \pm 4.27 (3–18)	<0.001
Etiology, n patients (%)			0.74
Idiopathic	17 (81)	16 (94)	
Biopsy-proven sarcoidosis	2 (5)	0 (0)	
Presumed sarcoidosis	1 (5)	1 (6)	
MS associated IU	1 (5)	0 (0)	
Complication, n eyes (%)			
Retinal vasculitis	33 (87)	0 (0)	N/A
Cystoid macular edema	11 (29)	0 (0)	N/A
Ocular hypertension	3 (8)	0 (0)	N/A
Glaucoma	4 (11)	2 (7)	0.68
Treatment			
Topical steroid, n eyes (%)	13 (34)	3 (10)	0.02
Systemic steroids, n patients (%)	14 (67)	1 (6)	< 0.001
Immunomodulatory drugs, n patients (%)	8 (38)	13 (76)	0.02
Biologic agents, n patients (%)	2 (10)	6 (35)	0.10

In terms of treatment received during the follow-up period, the rates of topical steroids and systemic steroids were significantly higher in the active IU group ($P = 0.02$ and $P < 0.001$, respectively). Use of immunomodulatory drugs was significantly higher in the quiescent group ($P = 0.02$). There was no significant difference in the use of biologic agents used between groups ($P = 0.10$).

Choroidal Parameter of the Groups at Baseline and Follow-up Within Each Group

In the active IU group, the mean CVI significantly increased from the baseline value of $66.50 \pm 3.40\%$

to $68.82 \pm 3.90\%$ at follow-up when the inflammation resolved ($P < 0.001$) (Fig. 2). The mean LA increased from $0.92 \pm 0.22 \text{ mm}^2$ to $0.98 \pm 0.22 \text{ mm}^2$ ($P = 0.003$) and the mean SA decreased from $0.48 \pm 0.15 \text{ mm}^2$ to $0.44 \pm 0.13 \text{ mm}^2$ ($P = 0.006$). No significant change in mean TCA and mean SCT were observed (both $P > 0.05$). An increase ($66.36\% \pm 3.45\%$ to $69.22\% \pm 3.86\%$; $P < 0.001$) in mean CVI was observed in 34 of 38 eyes (89%), whereas four eyes (11%) had a decrease in mean CVI from $67.69\% \pm 3.07\%$ to $66.02\% \pm 2.70\%$ ($P = 0.26$).

Among 38 eyes in active IU group, 10 eyes had a subsequent episode of flare after the resolution of inflammation. The mean CVI of these eyes

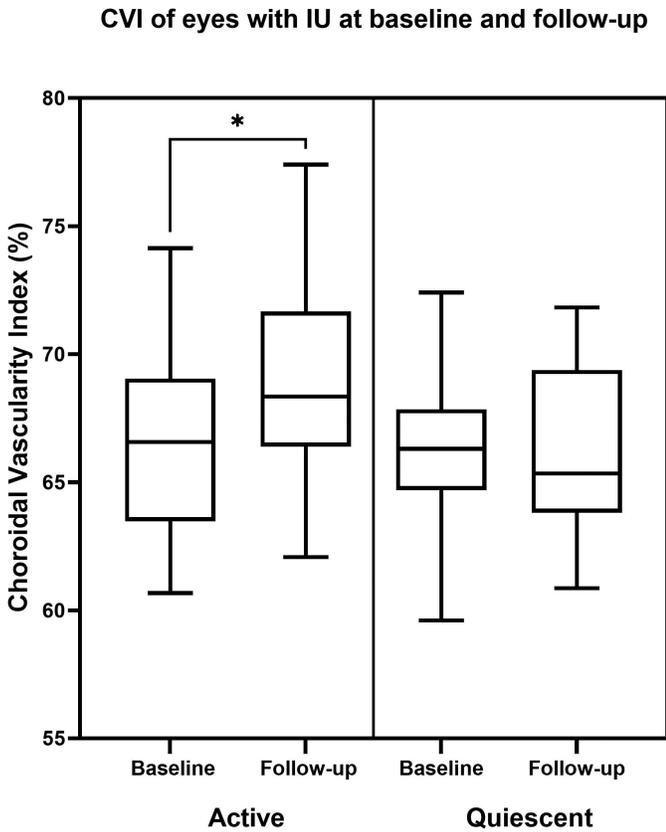


Figure 2. Box and Whisker plot CVI of eyes with intermediate uveitis at baseline and follow-up.

significantly decreased when the disease flared ($67.50\% \pm 3.88\%$ to $65.27\% \pm 3.30\%$; $P = 0.02$).

Change in CVI Based on Characteristics of Inflammation

In active eyes at follow-up, CVI increased significantly in both retinal vasculitis group ($66.23\% \pm 3.47\%$ to $67.86\% \pm 3.64\%$; $P = 0.02$) and nonretinal vasculitis group. ($66.83\% \pm 3.39\%$ to $70.00\% \pm 3.99\%$; $P < 0.001$). The increase in CVI at follow-up was also

observed in eyes with vitreous haze ($66.54\% \pm 3.66\%$ to $68.75\% \pm 3.83\%$; $P < 0.001$) and eyes without vitreous haze ($66.43\% \pm 2.99\%$ to $68.96\% \pm 4.19\%$; $P < 0.001$). Further data about choroidal measurements at baseline and follow-up visits in both groups are presented in [Table 2](#).

Comparison of Choroidal Parameters Between Groups

At baseline, no significant differences in choroidal parameters were observed between the active and quiescent IU groups. But, at follow-up, CVI was significantly higher in the active IU group compared with the quiescent IU group ($68.82\% \pm 3.90\%$ vs. $66.25\% \pm 3.13\%$; $P < 0.001$) after adjustment for covariates including disease duration and follow-up period. Adjusted SA was also significant lower in the active IU group ($0.44 \pm 0.13 \text{ mm}^2$ vs. $0.50 \pm 0.12 \text{ mm}^2$; $P < 0.001$). Aside from CVI and SA, no other choroidal parameters significantly differed between the two groups. Differences in choroidal parameters between groups are summarized in [Table 2](#).

Agreement Between Graders

Between the two independent observers, CVI and SCT measurement was noted with an ICC of 0.982 (95% confidence interval, 0.90–0.96) and 0.926 (95% confidence interval, 0.90–0.96), indicating excellent agreement between observers.

Discussion

In this retrospective cohort study, we used CVI to evaluate choroidal vascular changes in eyes with IU. In the active IU group, we found that the CVI significantly increased from baseline to follow-up. However, in the quiescent group, no change in CVI was observed from

Table 2. Comparison of Choroidal Vascular Parameters in Eyes With Intermediate Uveitis

	Active Group (n = 38)			Quiescent Group (n = 30)			P Value Between Groups	
	Baseline	Follow-up	P Value*	Baseline	Follow-up	P Value*	Baseline†	Follow-up‡
CVI (%)	66.50 ± 3.40	68.82 ± 3.90	<0.001	66.34 ± 3.19	66.25 ± 3.13	0.850	0.858	<0.001
TCA (mm ²)	1.41 ± 0.36	1.41 ± 0.32	0.829	1.45 ± 0.29	1.46 ± 0.28	0.572	0.713	0.083
LA (mm ²)	0.92 ± 0.22	0.98 ± 0.22	0.003	0.96 ± 0.18	0.97 ± 0.18	0.553	0.536	0.750
SA (mm ²)	0.48 ± 0.15	0.44 ± 0.13	0.006	0.49 ± 0.12	0.50 ± 0.12	0.383	0.817	<0.001
SCT (µm)	304.14 ± 74.07	312.91 ± 70.40	0.082	327.04 ± 49.40	334.40 ± 44.50	0.287	0.132	0.606

Statistically significant P values are reported in bold.

*Paired t-test.

†Unpaired t-test.

‡Analysis of covariance adjusted for each baseline choroidal parameter, age, disease duration, and follow-up period.

baseline to follow-up. To our knowledge, this is the first study evaluating longitudinal changes in the choroidal vasculature of patients with IU using CVI.

CVI is a two-dimensional measurement that accounts for both stromal and vascular changes of the choroid.¹⁸ Studies using CVI in various causes of uveitis showed that CVI can be used to identify longitudinal changes, particularly in posterior or panuveitis.^{6,8–11,19–21} However, longitudinal changes in CVI in patients with IU remain unknown.

Our results showed that eyes with active IU had a significant increase in mean CVI at follow-up compared to baseline. Further analysis revealed that a significant increase in mean LA and a significant decrease in mean SA accounted for this change.

Although the exact pathogenesis of IU is not fully understood, it is primarily thought to be CD4⁺ T-helper (Th) cell-mediated.^{22,23} We hypothesize that the activated T helper (Th) 1 and Th17 response is associated with the release of proinflammatory cytokines that may lead to secondary choroidal vasodilation as well as increased vascular permeability, resulting in an increase in caliber of choroidal vessels.²⁴ However, the magnitude of increase in diameter of choroidal vessels in IU may be minimal compared to the degree of choroidal expansion from extravasation of inflammatory cells, which thus may account for a relative reduction of choroidal vessel lumen volume. Our hypothesis is partly supported by histologic finding of pars planitis eye that small aggregation of lymphocytes was found in the peripheral choroidal stroma. However, the findings of choroidal vessels in this study was not described.¹² After the inflammation subsides, the choroidal vessels may expand, accounting for the relative increase in CVI. However, we speculate that a longer follow-up period may reveal further changes in CVI. With time, CVI may approach baseline as a consequence of a choroidal stromal remodeling process.

A post-treatment increase in CVI has also been observed in VKH patients. Liu et al.¹⁰ showed that CVI significantly increased after an anterior uveitis flare of VKH resolved ($72\% \pm 9\%$ vs. $75\% \pm 8\%$; $P = 0.01$). Kawano et al.²¹ also reported increased CVI in acute VKH at one week after steroid treatment. In both studies, the increase in CVI was attributed to a substantial reduction in the choroidal stroma area. However, in contrast, post-treatment decreases in CVI have also been noted. Agrawal et al.⁷ observed that CVI in eyes with posterior uveitis and panuveitis significantly decreased at three-month follow-up ($74.1\% \pm 4.7\%$ vs. $69.4\% \pm 4.8\%$; $P < 0.001$). Agrawal et al.⁸ also completed a retrospective review of 19 eyes with acute VKH and demonstrated that CVI was significantly reduced 6 to 12 months after receiving systemic steroid

treatment ($70.03\% \pm 1.93\%$ vs. $66.94\% \pm 1.82\%$; $P < 0.0001$). Jaisankar et al.⁹ demonstrated similar findings of a decreased CVI post-acute VKH treatment. In these studies, the increase in CVI was attributed to a reduction in stasis of blood flow in the choroidal stroma. Heterogeneity in the follow-up period and definition of disease activity may explain the conflicting reports of longitudinal change of CVI in VKH.

In the quiescent IU group, no significant changes in the CVI and other choroidal parameters were noted at follow-up. Well-controlled inflammation over the follow-up period likely accounts for this. Additionally, quiescent eyes had a longer disease duration compared to active eyes. Choroidal stromal and vascular areas in these eyes may have already become fibrotic and minimally affected by subclinical inflammation.

Comparing the baseline CVI between the active group and quiescent group revealed no statistically significant difference. This could be due to the heterogeneity between the two groups at baseline, particularly the difference in disease duration and treatment. Based on our results, we propose that CVI may be used as a biomarker to monitor treatment response in terms of relative change in CVI value rather than being used as an absolute parameter distinguishing disease activity.

Although we have shown that CVI was increased when active inflammation of IU resolved, no significant changes in SCT at baseline and follow-up was observed. First, SCT is known to be affected by ocular and systemic factors,²⁵ making it inaccurate in the longitudinal assessment of the choroid. Second, SCT may be less reliable than CVI for assessing specific choroidal and vascular changes because it relies only on a single vertical measurement. Thus SCT may be unable to detect the changes in choroidal vascularity in IU.

Limited imaging studies have described choroidal changes in IU. Géhl et al.²⁶ studied choroidal thickness using SD-OCT in different ETDRS subfields. They found that choroidal thickness in IU eyes was significantly lower in the nasal 6 mm quadrant compared to healthy controls, but the other quadrants lacked statistical significance. This finding is difficult to compare with our study because we used EDI-OCT, a superior imaging modality to the conventional SD-OCT for visualizing the choroidal-scleral junction.²⁷ Further support of choroidal involvement in IU was demonstrated by the OCT-A changes observed by Tian et al.,¹³ who showed reduced perfusion at the level of choriocapillaris IU eyes. Also, Wintergerst et al.¹⁴ revealed a heterogeneous flow in the choriocapillaris of eyes with IU, suggesting alterations in choroidal perfusion. However, subgroup analysis by disease

activity was absent in both studies. Furthermore, they were cross-sectional in nature.

Our methodology for CVI calculation provides increased standardization. Region of interest selection is crucial for accurate comparison between study groups. We used a fixed-line length nasally and temporally from the central fovea to define the TCA. Additionally, by limiting the number of vertices in our polygon, we reduced variability in region of interest selection without sacrificing accuracy, which may account for the excellent agreement in CVI between the two graders. With using CVI, intrarater agreement as well as intraeye reliability were also found to be high.^{6,28,29} Additionally, CVI can be obtained from publicly available software (ImageJ) and the technique is well described in previous literatures.^{6,30} For these reasons, CVI has shown to be a potential marker in terms of reproducibility and repeatability.

Nevertheless, we experienced some limitations of using CVI. Calculating CVI ultimately depends on OCT image quality. Delineating the choroid-scleral junction, particularly in eyes with thick choroid, can be challenging since the junction is sometimes poorly defined. Retinal blood vessels may cause shadowing artifacts; however, a technique has been suggested to compensate for these shadows.³¹ Ocular media opacities secondary to dense vitritis or dense cataract can limit visualization of the choroid further. SS-OCT would be an alternative imaging modality used to provide better image quality because of its longer wavelength and faster scanning speed compared to SD-OCT.³² Widefield EDI-OCT focusing on peripheral choroid may detect higher magnitude of change in CVI because IU tends to be involve the peripheral retina and ciliary body.^{3,33} Longitudinal changes in CVI should be interpreted with caution. The direction and magnitude of change in CVI relies on the proportion of both choroidal vascular and stroma components which depends on etiology, duration, and stage of disease. CVI could remain unaffected due to the proportionate decrease in both luminal and stromal area as a result of choroidal thinning.¹⁹ Therefore one should consider other choroidal parameters including LA, SA, TCA and choroidal thickness as performed in our study. These parameters may help elucidate pathological change of the choroid in the context of the choroidal vasculature and stroma.

There are several limitations in our study. First, a regular follow-up interval could not be determined because of the retrospective nature of the study. Second, our small sample size may have limited the power of the analysis and reduced the ability to assess different parameters including age, disease duration, and clinical signs of inflammation affecting CVI in IU.

Third, we did not consider other parameters that possibly affect either CVI or CT (e.g., axial length, diurnal variations).

In conclusion, we demonstrate that CVI increases when active inflammation in IU resolves while CVI remains unchanged at follow-up in quiescent IU. This finding suggests that CVI may be a useful non-invasive tool to monitor treatment response in IU. In addition, our findings highlight the choroidal vascular involvement even in diseases conventionally thought to not involve the choroid. These findings have potential implications in pathophysiology of disease, as well as therapeutic approaches. Nevertheless, further prospective studies with larger sample sizes and serial CVI measurements are needed to further support our findings.

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