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Peripapillary Choroidal Vascularity Outside the Macula in Patients With Central Serous Chorioretinopathy

Young Ho Kim[1], Boram Lee[1], Edward Kang[1], and Jaeryung Oh[1]

[1] Department of Ophthalmology, Korea University College of Medicine, Seoul, Korea

Correspondence: Jaeryung Oh, Department of Ophthalmology, Korea University College of Medicine, 73 Goryeodae-ro Sungbuk-ku, Seoul, 02841, Korea.
e-mails: ojr4991@korea.ac.kr, ojr4991@yahoo.co.kr

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Purpose: To investigate choroidal vascularity outside the macula in central serous chorioretinopathy (CSC).

Methods: Fifty normal controls and 103 patients with a history of CSC (31 with acute CSC, 32 with chronic CSC, and 40 with resolved CSC) were included. Using swept-source optical coherence tomography, we measured choroidal thickness (CT) and choroidal vascularity index (CVI) at the subfoveal and nasal peripapillary areas.

Results: Subfoveal CT in the acute CSC group was greater than that in all other groups (all $P < 0.05$). Peripapillary CT in the acute and chronic CSC groups was significantly greater than that in controls (all $P \leq 0.005$). However, subfoveal and peripapillary CT in the resolved CSC group was not different from controls. Subfoveal CVI in the acute group (64.71% $\pm$ 2.68%) was higher than that in controls (61.68% $\pm$ 5.68%) ($P = 0.015$). Peripapillary CVIs in the acute (67.35% $\pm$ 6.04%) and chronic groups (64.90% $\pm$ 5.31%) were higher than controls (54.57% $\pm$ 7.02%) (all $P < 0.001$). Subfoveal CVI in the resolved CSC group was not different from controls ($P = 0.252$), whereas peripapillary CVI (62.61% $\pm$ 6.03%) was higher ($P < 0.001$).

Conclusions: Unlike CT, CVI outside the macula was increased in all eyes with both current and past history of CSC. These findings suggest that the choroidal vascularity outside the macula may represent choroidal characteristics in addition to the subfoveal area.

Translational Relevance: Peripapillary CVI outside the macula may provide additional information beyond what is known through subfoveal choroid studies.

Introduction

Central serous chorioretinopathy (CSC) is a chorioretinal disease characterized by a serous neurosensory retinal detachment at the macula.[1–3] Various retinal imaging studies have highlighted the contribution of the choroid in CSC pathogenesis.[2,3] After the introduction of optical coherence tomography (OCT), imaging biomarkers, including quantitative measurement of subretinal choroidal fluid, hyperreflective dots, and choroidal thickness (CT), have also been presented.[4] Choroidal changes in CSC have been reported and are characterized by increased CT or dilated choroidal vessels.[5–10] Although the subfoveal CT has been accepted as a surrogate to characterize the choroid in patients with CSC, it is known to be affected by many factors.[11–15] In a recent study,[16] choroidal vascularity index (CVI) was presented as a quantitative method to measure choroidal vascularity. The CVI has been measured in several retinal and choroidal diseases,[16–20] such as uveitis, age-related macular degeneration, retinal vascular occlusion, diabetic retinopathy, and CSC. Agrawal et al.[21] reported that CVI remained unaffected, whereas CT was affected by many factors. In addition, they suggested that the CVI is a more robust marker of choroidal diseases. Breher et al.[22] showed that CVI had little fluctuation between subfields, unlike CT. In recent studies,[4,23–25] increased CVI has been noted in acute and chronic CSC; however, further studies are required to clarify the relationship between these two biomarkers obtained from OCT imaging, CT, and CVI, and their roles in pathophysiology.

It has been suggested that abnormal choroidal circulation and choroidal vascular hyperpermeability are associated with CSC.[2,5] Although the choroid is the posterior portion of the uveal tract covering the posterior two-thirds of the eye,[26] most previous studies have focused on the subfoveal choroid. However, the choroid at the subfoveal area may not be representative of the entire choroid.[27,28] Recently, changes in peripapillary CT and vascularity, as well as subfoveal CT, have been reported in various chorioretinal diseases.[28–33] A previous study showed that the increased CT in patients with CSC is not limited to the macular area; however, few studies have examined variations of peripapillary CVI in CSC.

In this study, we hypothesized that peripapillary CVI outside the macula in patients with various stages of CSC would differ from that of normal controls. We also compared CT and CVI in both the subfoveal and nasal peripapillary areas among patients with CSC and normal controls.

Methods

This study was approved by the institutional review board of Korea University Hospital, Seoul, Korea, and adhered to the tenets of the Declaration of Helsinki.

Subjects

We included subjects with a current or past history of CSC from the swept-source OCT (SS-OCT) database between May 2015 and October 2020. We excluded eyes with retinal vascular diseases with peripapillary involvement or macular edema; a history of vitreoretinal surgery, laser therapy, photodynamic therapy, or injection of anti-vascular endothelial growth factor; and severe glaucoma. We also included normal controls with normal fundus from the database. For normal controls, we included only subjects without chorioretinal disease except for idiopathic epiretinal membrane in the fellow eye, and we excluded subjects with any drusen or pigmentary changes in any eye. We also excluded eyes with pathologic myopia. Data from medical records, including sex, age, best-corrected visual acuity, refractive errors, history of diabetes mellitus, and hypertension, were reviewed. At presentation, all patients underwent a comprehensive examination, including fundus photography, SS-OCT (DRI OCT Triton; Topcon Corporation, Tokyo, Japan), OCT angiography (DRI OCT Triton; Topcon Corporation), and fluorescein angiography and indocyanine green angiography (Spectralis HRA2; Heidelberg Engineering, Heidelberg, Germany). The collected images were analyzed independently by two experienced retinal specialists (Y.H.K. and B.R.L.). CSC was diagnosed when serous neurosensory retinal detachment was identified on SS-OCT, accompanied by fluorescein leakage at the level of the retinal pigment epithelium (RPE) on fluorescein angiography. Only one eye was included when both eyes were diagnosed with CSC. Acute and chronic CSC were defined as described in previous studies. CSC was diagnosed as acute CSC when acute neuroepithelium detachment associated with pachychoroid showed spontaneous complete resolution of the subretinal fluid within 3 to 6 months.[3,34] Chronic CSC was defined as the presence of visual symptoms for at least 6 months, with documented clinical features of CSC, including changes in macular subretinal fluid and RPE, documented on OCT imaging.[35] Resolved CSC was defined when the subject had a history of CSC that had resolved at least 12 months ago.

Measurement on SS-OCT

Using SS-OCT, a 9-mm horizontal line scan averaging from 96 B-scan images was performed, and a volume scan was acquired over a 12 × 9-mm area consisting of 256 horizontal B-scans. The volume scan was centered between the fovea and optic disc and covered the macular and peripapillary regions.

Using the manual caliper tool of the built-in software, the CT was measured at the subfovea and nasal peripapillary areas, using a previously reported method.[36–38] We measured subfoveal CT using a 9-mm horizontal line scan passing through the fovea and peripapillary CT using a 12-mm volume scan image passing through the center of the optic disc. CT was defined as the vertical perpendicular distance from Bruch's membrane to the innermost hyperreflective line of the choroidoscleral interface. Subfoveal CT was manually measured at the foveola. For the measurement of peripapillary CT, a circular grid (3.4 mm in diameter) used for retinal nerve fiber layer (RNFL) analysis was automatically placed at the center of the optic nerve on the fundus photograph (Fig. 1E). By clicking on the nasal rim of the RNFL grid (3 o'clock or 9 o'clock position) on the fundus photograph, a vertical line was placed automatically on the B-scan image passing through the center of the optic disc (Fig. 1F). The cross point between this line and Bruch's membrane was used as the reference point from which the peripapillary CT was measured.

Both SS-OCT images were exported to measure the subfoveal and peripapillary CVI. CVI, defined as the ratio of luminal area to total choroidal area, was

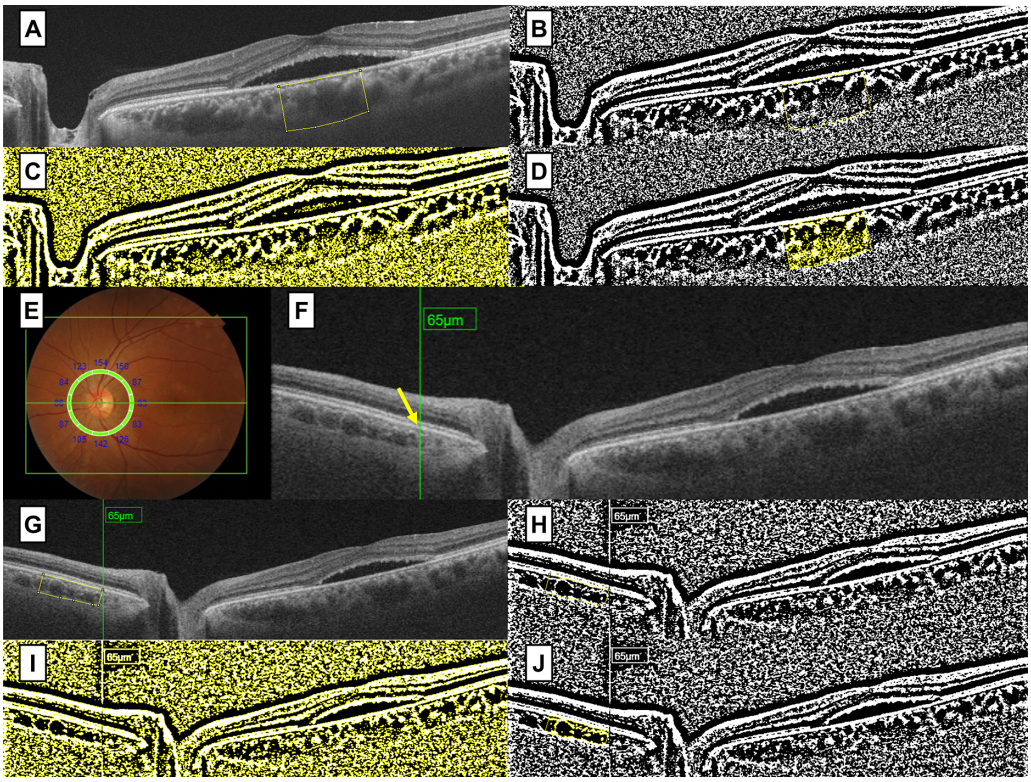

Figure 1. Measurements of subfoveal and peripapillary CVI. Subfoveal CVI is measured using a 9-mm line scan, which is centered on the fovea (**A–D**), and peripapillary CT is measured using a 12 × 9-mm volume scan image (**E–J**). (**A**, **G**) Using the polygon tool, a region of interest (ROI) with a width of 1500 μm is selected. (**E**) For the selection of the ROI in the nasal peripapillary area, the circular grid (3.4 mm in diameter) used for peripapillary RNFL analysis is automatically placed at the center of the optic nerve with manual adjustment. (**F**) By clicking on the nasal rim of the RNFL circular grid, a vertical line is placed on the B-scan image passing through the center of the RNFL circular grid. The cross point between this line and Bruch's membrane is used as the reference point (*yellow arrow*) from which the peripapillary CVI is measured. (**B**, **H**) Using the Niblack auto-threshold method, image binarization is performed after conversion to 8-bit images. (**C, I**) The color threshold tool is applied after the image is converted back to an RGB image. (**D**, **J**) Merged images with initially selected total choroidal area.

measured on the SS-OCT images using methods previously described by Sonoda et al.[39,40] and Agrawal et al.[16] with some modifications (Fig. 1).[41] In brief, the same OCT images for the measurement of subfoveal and peripapillary CT were imported into ImageJ software (National Institutes of Health, Bethesda, MD). Prior to image binarization, the region of interest (ROI) was selected using a polygon tool to measure the total choroidal area. For the measurement of subfoveal CVI, a width of 1500 μm, centered at the fovea, was manually selected (Fig. 1A). For the measurement of peripapillary CVI, a width of 1500 μm outside the nasal side from the previously determined reference point for peripapillary CT measurement was selected as the ROI to measure the peripapillary CVI (Fig. 1G). For both subfoveal and peripapillary CVI measurements, the inner border of the ROI was defined as Bruch's membrane, and the outer border was defined as the choroidoscleral junction. The total subfoveal and peripapillary choroidal areas were then computed.

For image binarization, OCT images were converted to 8-bit images, and an auto-threshold was applied using the Niblack method to demarcate the choroidal vascular and stromal areas (Figs. 1B, 1H). To select dark pixels, the image was converted back to a red, green, and blue (RGB) image, and the color threshold tool was applied (Figs. 1C, 1I). Using the "AND" operation, it was merged with the initially selected total choroidal area (Figs. 1D, 1J). With the merged image, the dark pixel area representing the luminal areas was determined and divided by the total choroidal area to calculate the CVI.

Two experts (Y.H.K. and B.R.L.) performed the measurements without patient information, and the mean values of the measurements obtained by the two examiners were used in the analysis. The interobserver intraclass correlation coefficients (ICCs) for the subfoveal and peripapillary CTs were 0.981 (95% confidence interval [CI], 0.973–0.986) and 0.980 (95% CI, 0.972–0.985), respectively. The ICCs for the subfoveal

and peripapillary CVIs were 0.961 (95% CI, 0.947–0.972) and 0.963 (95% CI, 0.948–0.973), respectively. All ICCs were greater than 0.90 and showed excellent repeatability.

Statistical Analysis

All statistical analyses were performed using SPSS Statistics 20.0 (IBM Corp., Armonk, NY). The baseline characteristics were compared using the independent *t*-test and paired *t*-test for continuous variables and the χ^2 test for categorical variables. Linear correlations among baseline characteristics were analyzed using Pearson's correlation test. To assess differences in the measurements between groups, a one-way analysis of variance (ANOVA) was performed using post hoc tests with Bonferroni correction. To adjust for age, analyses of covariance (ANCOVA) were also performed, and the estimated marginal means of CT and CVI and their ratios were calculated and compared among groups. Results were considered statistically significant at $P < 0.05$.

Results

General Characteristics

A total of 103 eyes in 103 patients with a history of CSC and 50 eyes in normal controls were included in this study (Table 1). The mean age of patients with a history of CSC was 53.7 ± 11.4 years, and that of normal controls was 55.9 ± 11.4 years ($P = 0.256$). Sex was not significantly different between patients with and without a history of CSC ($P = 0.116$).

Thickness and Vascular Index of the Subfoveal and Peripapillary Choroid

Subfoveal CT was greater than peripapillary CT in both normal controls ($P < 0.001$; 95% CI, 101.5–143.1) and eyes with a history of CSC ($P < 0.001$; 95% CI, 127.2–161.0). Subfoveal CT was also correlated with peripapillary CT in both groups ($r = 0.557$, $P < 0.001$; $r = 0.714$, $P < 0.001$, respectively) (Fig. 2). Subfoveal CVI was also higher than peripapillary CVI in normal controls ($P < 0.001$; 95% CI, 5.324–8.885); however, there was no difference in eyes with a history of CSC ($P = 0.184$). In both groups, subfoveal CVI was correlated with peripapillary CVI ($r = 0.530$, $P < 0.001$; $r = 0.404$, $P < 0.001$, respectively).

In normal controls, subfoveal CT correlated with subfoveal CVI ($r = 0.415$, $P = 0.003$), but peripapillary CT did not correlate with peripapillary CVI ($r = 0.236$, $P = 0.098$). However, in eyes with a history of CSC, subfoveal CT did not correlate with subfoveal CVI ($r = -0.017$, $P = 0.862$), whereas peripapillary CT correlated with peripapillary CVI ($r = 0.438$, $P < 0.001$).

Correlation of CT and CVI With Age

In normal controls, both subfoveal and peripapillary CT were correlated with age ($r = -0.295$, $P = 0.037$; $r = -0.350$, $P = 0.013$, respectively) (Fig. 3). However, subfoveal or peripapillary CVI did not correlate with age ($r = -0.098$, $P = 0.499$; $r = 0.030$, $P = 0.836$, respectively).

In eyes with a history of CSC, both subfoveal and peripapillary CT were correlated with age ($r = -0.335$, $P = 0.001$; $r = -0.277$, $P = 0.005$, respectively). Subfoveal CVI did not correlate with age ($P = 0.103$),

Table 1. Baseline Characteristics of Normal Control and Patients With a History of CSC

Variables	Normal Control	Patients With a History of CSC	*P*
Number, *n*	50	103	
Age (y), mean ± SD	55.9 ± 11.4	53.7 ± 11.4	0.256
Sex (male, female), *n*	28, 22	71, 32	0.116
Diabetes, *n* (%)	7 (14.0)	12 (11.7)	0.679
Hypertension, yes, *n* (%)	19 (38.0)	27 (26.2)	0.136
Subfoveal CT (µm), mean ± SD	261.1 ± 87.1	346.9 ± 123.4	<0.001[a]
Peripapillary CT (µm), mean ± SD	138.8 ± 59.4	202.8 ± 91.3	<0.001[a]
Ratio of subfoveal CT to peripapillary CT, mean ± SD	2.09 ± 0.82	1.86 ± 0.62	0.092
Subfoveal CVI (%), mean ± SD	61.68 ± 5.68	64.00 ± 3.43	0.009[a]
Peripapillary CVI (%), mean ± SD	54.57 ± 7.02	64.75 ± 6.09	<0.001[a]
Ratio of subfoveal CVI to peripapillary CVI, mean ± SD	1.141 ± 0.125	0.995 ± 0.089	<0.001[a]

[a] $P < 0.05$ by independent *t*-test or χ^2 test.

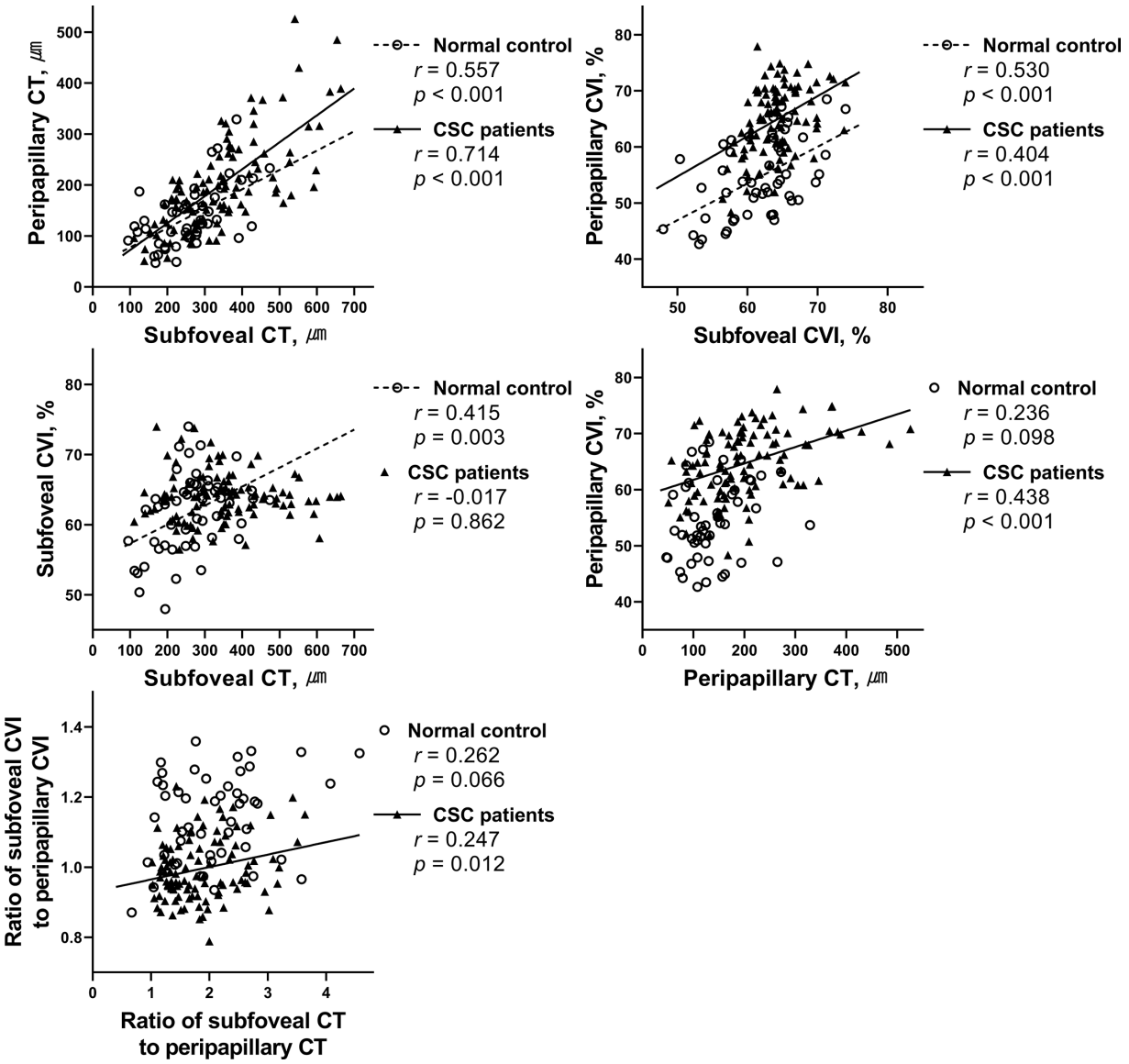

Figure 2. Correlation among subfoveal and peripapillary CT and CVI and their ratios in normal control and patients with a history of central serous chorioretinopathy.

whereas peripapillary CVI correlated with age ($r = -0.302$, $P = 0.002$).

Comparison of CT Among Groups

A total of 134 eyes were classified into four groups: 50 normal controls, 31 acute CSC, 32 chronic CSC, and 40 resolved CSC. The mean age was different among the groups ($P = 0.003$) (Table 2). A post hoc test with Bonferroni adjustment revealed that patients in the acute CSC group were younger than those in the control and chronic CSC groups ($P = 0.017$ and $P = 0.002$, respectively) (Supplementary Table S1). However, there were no differences in age among subjects in the normal control, chronic CSC, and resolved CSC groups. Distribution of sex did not differ among the groups ($P = 0.242$).

Subfoveal CT in the acute CSC group (415.4 ± 127.6 μm) was greater than that in the normal control group (261.1 ± 87.1 μm; $P < 0.001$), chronic CSC group (335.7 ± 100.3 μm; $P = 0.021$), and resolved CSC group (302.8 ± 116.0 μm; $P < 0.001$) (Fig. 4A, Supplementary Table S1). Subfoveal CT in the chronic CSC group was also greater than that in the normal control group ($P = 0.014$) but was not different from that in the resolved CSC group ($P > 0.999$). Peripapillary CT in the acute

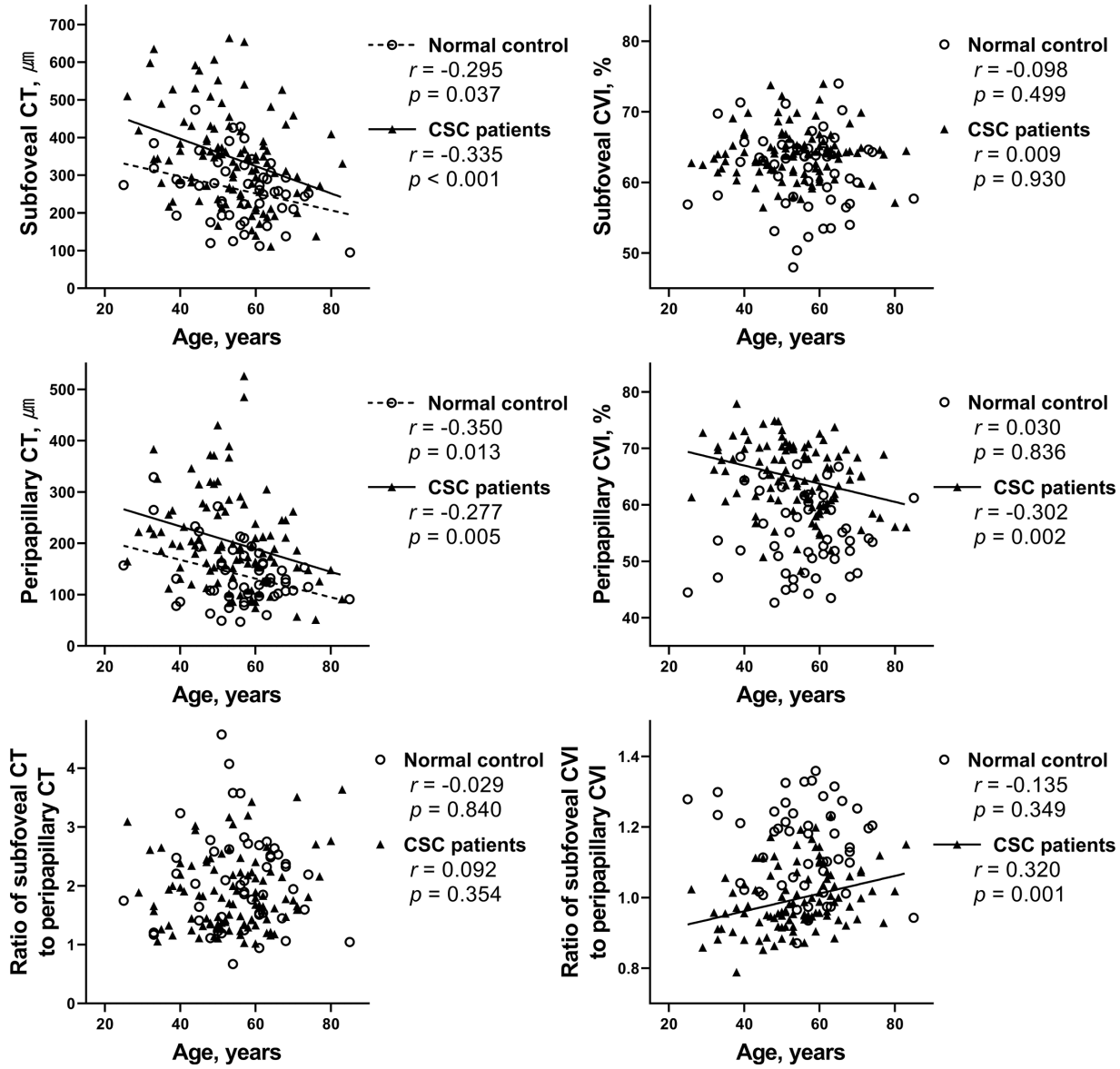

Figure 3. Correlation among various choroidal variables and age in normal control and patients with a history of CSC.

CSC (227.9 ± 104.2 μm) and chronic CSC (227.4 ± 85.3 μm) groups was significantly greater than that in the normal control group (138.8 ± 59.4 μm) and resolved CSC group (163.7 ± 71.4 μm) ($P < 0.001$ and $P = 0.005$ for the acute CSC group; $P < 0.001$ and $P = 0.005$ for the chronic CSC group), whereas there was no difference between the acute and chronic CSC groups ($P > 0.999$) or between the normal control and resolved CSC groups ($P = 0.826$). The ratio of subfoveal CT to peripapillary CT in the chronic CSC group (1.53 ± 0.35) was significantly lower than that in the normal control group (2.09 ± 0.82; $P = 0.002$), acute CSC group (2.01 ± 0.60; $P = 0.032$), and resolved CSC group (2.01± 0.71; $P = 0.017$).

Comparison of CVI Among Groups

Subfoveal CVI ($P = 0.013$), peripapillary CVI ($P < 0.001$), and the ratio of subfoveal CVI to peripapillary CVI ($P < 0.001$) were significantly different among the different groups (Table 3). Subfoveal CVI in the acute CSC group (64.71% ± 2.68%) was higher than that in the normal control (61.68% ± 5.68%; $P = 0.015$) (Fig. 4B, Supplementary Table S2). Subfoveal CVI in the chronic CSC group (63.90% ± 2.54%) and resolved CSC group (62.61% ± 6.03%) was not significantly different from that in normal controls. Peripapillary CVI in the acute CSC group (67.35 ± 6.04%), chronic CSC group (64.90% ± 5.31%), and resolved CSC group

Table 2. Age, Sex Distribution, and Subfoveal and Peripapillary CT of Normal Control and Various Groups of Patients With a History of CSC

		Patients With a History of CSC ($N = 103$)			
	Normal Control	Acute CSC	Chronic CSC	Resolved CSC	*P*
Number, *n*	50	31	32	40	—
Age (y), mean ± SD	55.9 ± 11.4	48.3 ± 10.1	58.4 ± 8.3	54.1 ± 12.9	0.003[a]
Sex (male, female), *n*	28, 22	20, 11	25, 7	26, 14	0.242
Subfoveal CT (μm), mean ± SD	261.1 ± 87.1	415.4 ± 127.6	335.7 ± 100.3	302.8 ± 116.0	<0.001[a]
Peripapillary CT (μm), mean ± SD	138.8 ± 59.4	227.9 ± 104.2	227.4 ± 85.3	163.7 ± 71.4	<0.001[a]
Ratio of subfoveal CT to peripapillary CT, mean ± SD	2.09 ± 0.82	2.01 ± 0.60	1.53 ± 0.35	2.01 ± 0.71	0.002[a]

[a]$P < 0.05$ by ANOVA.

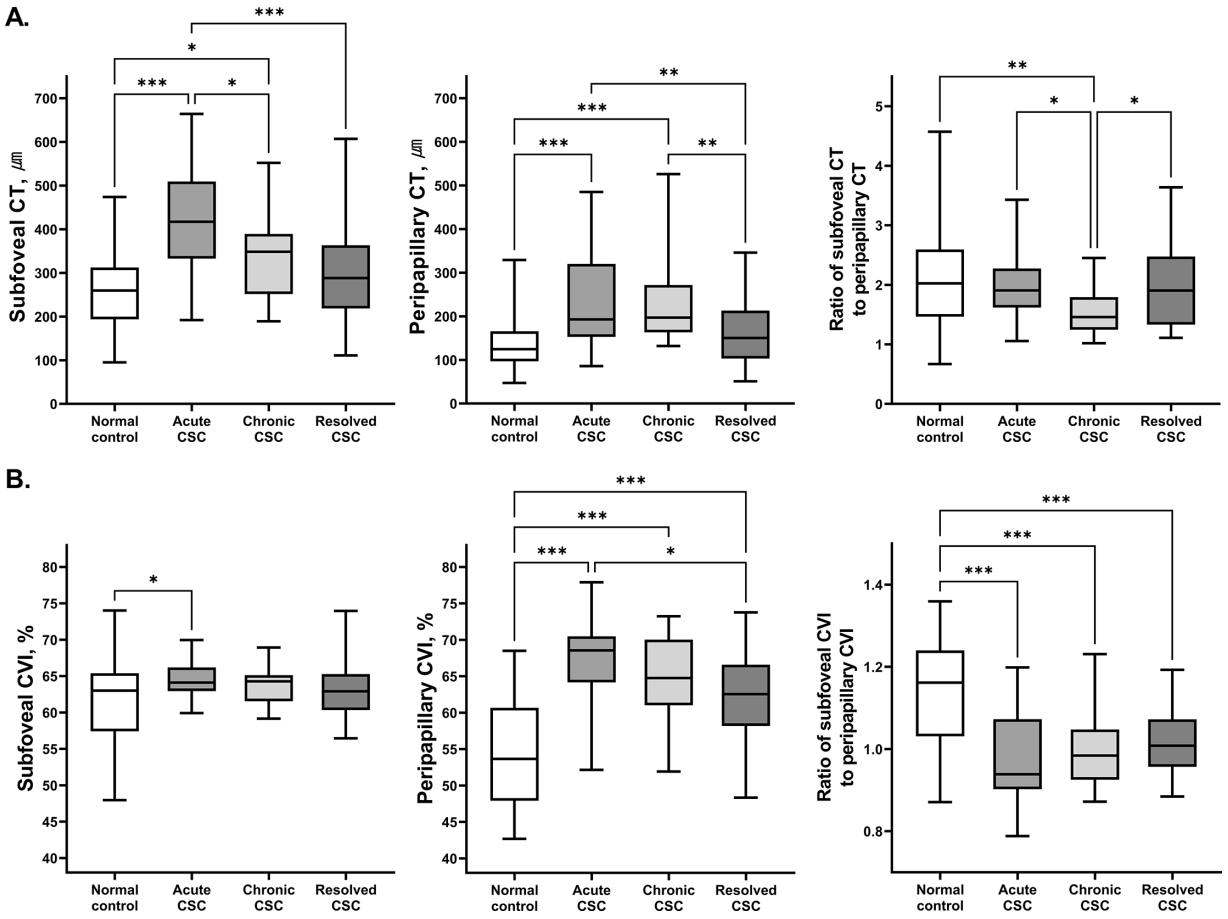

Figure 4. Multiple comparisons of various variables of CT (**A**) and CVI (**B**) among the different groups. One-way analysis of variance was performed using post hoc tests with Bonferroni correction. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

(62.61% ± 6.03%) was significantly higher than that in normal controls (54.57% ± 7.02%) (all $P < 0.001$). Peripapillary CVI in the resolved CSC group was lower than that in the acute CSC group ($P = 0.011$). The ratio of subfoveal CVI in the acute CSC group (0.969 ± 0.106), chronic CSC group (0.990 ± 0.082), and resolved CSC group (1.020 ± 0.075) were significantly lower than that in the normal control (1.141 ± 0.125) (all $P < 0.001$).

Analyses of Covariance

In the total 153 patients, ANCOVA including age and groups showed that both subfoveal CT ($P = 0.001$) and peripapillary CT ($P < 0.001$) were significantly affected by age, but the ratio of subfoveal CT to peripapillary CT ($P = 0.167$) and CVIs were not affected by age (Table 4). After adjustment for age, there were significant differences in subfoveal CT

Table 3. Subfoveal and Peripapillary CVIs of Normal Control and Various Groups of Patients With a History of CSC

		Patients With a History of CSC ($N = 103$)			
	Normal Control	Acute CSC	Chronic CSC	Resolved CSC	*P*
Number, *n*	50	31	32	40	—
Subfoveal CVI (%), mean ± SD	61.68 ± 5.68	64.71 ± 2.68	63.90 ± 2.54	63.55 ± 4.41	0.013[a]
Peripapillary CVI (%), mean ± SD	54.57 ± 7.02	67.35 ± 6.04	64.90 ± 5.31	62.61 ± 6.03	<0.001[a]
Ratio of subfoveal CVI to peripapillary CVI, mean ± SD	1.141 ± 0.125	0.969 ± 0.106	0.990 ± 0.082	1.020 ± 0.075	<0.001[a]

[a] $P < 0.05$ by ANOVA.

Table 4. ANCOVA for Risk Factors of Changes in CT and CVI and Their Ratios in Eyes With Normal Fundus and Various Groups of CSC

Source of Variation	Sum of Squares	df	Mean of Squares	*F*	*P*
Subfoveal CT (µm)					
Age	130,628.367	1	130,628.367	12.345	0.001[a]
Groups	366,601.984	3	122,200.661	11.549	<0.001[a]
Peripapillary CT (µm)					
Age	88,039.753	1	88,039.753	15.610	<0.001[a]
Groups	220,233.187	3	73,411.062	13.016	<0.001[a]
Ratio of subfoveal CT to peripapillary CT					
Age	0.867	1	0.867	1.926	0.167
Groups	7.435	3	2.478	5.507	0.001[a]
Subfoveal CVI (%)					
Age	1.017	1	1.017	0.055	0.816
Groups	197.347	3	65.782	3.532	0.016[a]
Peripapillary CVI (%)					
Age	137.367	1	137.367	3.591	0.060
Groups	3624.687	3	1208.229	31.585	<0.001[a]
Ratio of subfoveal CVI to peripapillary CVI					
Age	0.022	1	0.022	2.122	0.147
Groups	0.723	3	0.241	23.630	<0.001[a]

df, degrees of freedom.
[a] $P < 0.05$ by ANCOVA.

($P < 0.001$), peripapillary CT ($P < 0.001$), and the ratio of subfoveal CT to peripapillary CT ($P = 0.001$) among the four groups (Supplementary Tables S3 and S4). The results were similar to those before adjustment for age, except for subfoveal CT. The difference in subfoveal CT between acute and chronic CSC was not significant ($P = 0.321$).

Discussion

Many studies have shown variations in subfoveal CVI. Breher et al.[22] reported that CVI showed little fluctuation between early treatment diabetic retinopathy study subfields in normal subjects, unlike CT, which demonstrated thinning toward the peripheral choroid. However, Singh et al.[42] reported that CVI showed significant regional variation, with the macular segment showing the lowest CVI and nasal segments the highest CVI in both CSC and fellow eyes. In this study, we measured the CVI at the subfovea and peripapillary area outside the macula in normal subjects and patients with a history of CSC. In both normal and CSC subjects, peripapillary CVI outside the macula was correlated with subfoveal CVI. Although the peripapillary CVI was lower than the subfoveal CVI in normal subjects, there was no difference between peripapillary and subfoveal CVI in patients with a history of CSC. These findings suggest that variation in choroidal vascularity between the macula and outside the macula exists in normal subjects and patients with a history of CSC.

In this study, subfoveal CVI was higher in patients with acute CSC than in normal controls, which

is consistent with previous studies,[4,23,24] although the difference in subfoveal CVI between the other groups was not significant in our patients. However, we showed that peripapillary CVI also increased in the acute, chronic, and resolved CSC groups. These findings suggest that acute manifest CSC occurs in patients with higher CVI both within and outside the macula, especially when the subfoveal CVI is increased. Subfoveal CVI in the resolved CSC group was not different from that in normal controls. However, peripapillary CVI was higher in the resolved CSC group than in the normal control group. These results differed from the findings that subfoveal and peripapillary CTs in the resolved CSC group did not differ from those in normal controls. These findings suggest that choroidal vascularity outside the macula may represent choroidal characteristics in addition to the subfoveal area.

In our study, subfoveal and peripapillary CVIs were not correlated with age in normal subjects. These findings are different from the findings that both subfoveal and peripapillary CTs were inversely correlated with age.[28,33,43,44] These results suggest that the measurement of subfoveal and peripapillary CVI may provide more stable choroidal characteristics than other parameters such as subfoveal CT and peripapillary CT. In a previous study, Suh et al.[45] showed that choroidal vascularity was not associated with peripapillary atrophy, whereas choroidal thinning was associated with peripapillary atrophy. In addition, Singh et al.[27] showed that nasal peripapillary CVI had no diurnal variation, whereas subfoveal CT and CVI had a significant diurnal variation in amplitude. These findings imply that the study of the peripapillary choroidal vascularity outside the macula may provide additional information in addition to what is known through the subfoveal choroid studies.

In the current study, we measured the CT in the macula and outside the macula. Consistent with a previous study,[28] the macular choroid was thickened in the acute and chronic CSC groups compared with normal controls. In addition, the peripapillary choroid outside the macula was also more thickened in the acute and chronic CSC groups than in normal controls. We previously focused on the peripapillary choroid outside the macula, and the nasal peripapillary choroid was significantly thickened in acute CSC patients compared with normal controls.[28] In the current study, we found that the peripapillary choroid outside the macula was also thickened in the chronic CSC group. In addition, the ratio of subfoveal CT to peripapillary CT in the chronic CSC group was lower than that in the normal control, acute CSC, and resolved CSC groups. These findings suggest that the chronic CSC group had diffuse choroidal thickening both within and outside the macula. Increased ocular perfusion pressure and altered choroidal blood flow regulation have been suggested as risk factors for chronic CSC in previous studies.[46,47] The findings of the current study—diffuse choroidal thickening and diffuse increased choroidal vascularity—may suggest that the increased perfusion or abnormal flow regulation is not limited to the macular area.

Several studies have been conducted to identify demographic, genetic, and clinical factors to predict the clinical course and prognosis of CSC. Among the proposed factors, age at presentation is one of the most consistent factors, and older age at presentation is reported to be associated with chronic CSC.[3,48–50] In this study, the mean age of the acute CSC group was lower than that of the chronic CSC group, consistent with previous studies.[3,48–50] Recently, several studies have been conducted to predict the disease course of CSC with various parameters of OCT images.[49–52] However, there is still a limitation in distinguishing the episode duration as acute or chronic at the initial presentation by age or OCT imaging parameters.[3,49–52] In this study, we measured CT and CVI with OCT images of acute and chronic CSC patients at the initial visit. Although peripapillary CT did not differ, the ratio of subfoveal CT to peripapillary CT in the chronic CSC group was lower than that in the acute CSC group. These results suggest that the ratio of subfoveal CT to peripapillary CT can be an important additional choroidal characteristic to distinguish between acute and chronic CSC groups.

This study has several limitations. First, in this retrospective study, only a small number of CSC patients were included in each group. Further studies with larger sample sizes are needed to confirm our findings. Second, because CT was measured manually, there may be errors in measurement, although such measurements have been acknowledged as having high reproducibility. Third, measurement of CT and CVI in the nasal retina far from the optic disk was not performed. Further prospective studies measuring the nasal retinal CT are needed.

Conclusions

Choroidal vascularity outside the macula was increased in all eyes with both current and a past history of CSC. Acute manifest CSC occurs in patients with higher CVI both within and outside the macula, especially when subfoveal CVI is increased. CVI, both within and outside the macula, did not vary with age

or sex in normal subjects, unlike CT. These findings suggest that choroidal vascularity outside the macula may represent choroidal characteristics, in addition to the subfoveal area.

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References

1. Gass JD. Pathogenesis of disciform detachment of the neuroepithelium. *Am J Ophthalmol.* 1967;63(suppl 3):1–139.
2. Nicholson B, Noble J, Forooghian F, Meyerle C. Central serous chorioretinopathy: update on pathophysiology and treatment. *Surv Ophthalmol.* 2013;58(2):103–126.
3. Daruich A, Matet A, Dirani A, et al. Central serous chorioretinopathy: recent findings and new physiopathology hypothesis. *Prog Retin Eye Res.* 2015;48:82–118.
4. Nkrumah G, Maltsev DS, Manuel PA, et al. Current choroidal imaging findings in central serous chorioretinopathy. *Vision.* 2020;4(4):44.
5. Guyer DR, Yannuzzi LA, Slakter JS, Sorenson JA, Ho A, Orlock D. Digital indocyanine green videoangiography of central serous chorioretinopathy. *Arch Ophthalmol.* 1994;112(8):1057–1062.
6. Spaide RF, Goldbaum M, Wong DW, Tang KC, Iida T. Serous detachment of the retina. *Retina.* 2003;23(6):820–846.
7. Imamura Y, Fujiwara T, Margolis R, Spaide RF. Enhanced depth imaging optical coherence tomography of the choroid in central serous chorioretinopathy. *Retina.* 2009;29(10):1469–1473.
8. Kim SW, Oh J, Kwon SS, Yoo J, Huh K. Comparison of choroidal thickness among patients with healthy eyes, early age-related maculopathy, neovascular age-related macular degeneration, central serous chorioretinopathy, and polypoidal choroidal vasculopathy. *Retina.* 2011;31(9):1904–1911.
9. Maruko I, Iida T, Sugano Y, Ojima A, Sekiryu T. Subfoveal choroidal thickness in fellow eyes of patients with central serous chorioretinopathy. *Retina.* 2011;31(8):1603–1608.
10. Spaide RF, Ryan EH, Jr. Loculation of fluid in the posterior choroid in eyes with central serous chorioretinopathy. *Am J Ophthalmol.* 2015;160(6):1211–1216.
11. Brown JS, Flitcroft DI, Ying GS, et al. In vivo human choroidal thickness measurements: evidence for diurnal fluctuations. *Invest Ophthalmol Vis Sci.* 2009;50(1):5–12.
12. Ikuno Y, Kawaguchi K, Nouchi T, Yasuno Y. Choroidal thickness in healthy Japanese subjects. *Invest Ophthalmol Vis Sci.* 2010;51(4):2173–2176.
13. Mansouri K, Medeiros FA, Marchase N, Tatham AJ, Auerbach D, Weinreb RN. Assessment of choroidal thickness and volume during the water drinking test by swept-source optical coherence tomography. *Ophthalmology.* 2013;120(12):2508–2516.
14. Sizmaz S, Küçükerdönmez C, Pinarci EY, Karalezli A, Canan H, Yilmaz G. The effect of smoking on choroidal thickness measured by optical coherence tomography. *Br J Ophthalmol.* 2013;97(5):601–604.
15. Ahn J, Ahn SE, Yang KS, Kim SW, Oh J. Effects of a high level of illumination before sleep at night on chorioretinal thickness and ocular biometry. *Exp Eye Res.* 2017;164:157–167.
16. Agrawal R, Salman M, Tan KA, et al. Choroidal vascularity index (CVI)–a novel optical coherence tomography parameter for monitoring patients with panuveitis? *PLoS One.* 2016;11(1):e0146344.
17. Keenan TD, Klein B, Agrón E, Chew EY, Cukras CA, Wong WT. Choroidal thickness and vascularity vary with disease severity and subretinal drusenoid deposit presence in nonadvanced age-related macular degeneration. *Retina.* 2020;40(4):632–642.
18. Bakthavatsalam M, Ng DS, Lai FH, et al. Choroidal structures in polypoidal choroidal vasculopathy, neovascular age-related maculopathy, and healthy eyes determined by binarization of swept source optical coherence tomographic images. *Graefes Arch Clin Exp Ophthalmol.* 2017;255(5):935–943.
19. Aribas YK, Hondur AM, Tezel TH. Choroidal vascularity index and choriocapillary changes in retinal vein occlusions. *Graefes Arch Clin Exp Ophthalmol.* 2020;258(11):2389–2397.

20. Kim M, Ha MJ, Choi SY, Park YH. Choroidal vascularity index in type-2 diabetes analyzed by swept-source optical coherence tomography. *Sci Rep.* 2018;8(1):70.
21. Agrawal R, Gupta P, Tan KA, Cheung CM, Wong TY, Cheng CY. Choroidal vascularity index as a measure of vascular status of the choroid: measurements in healthy eyes from a population-based study. *Sci Rep.* 2016;6:21090.
22. Breher K, Terry L, Bower T, Wahl S. Choroidal biomarkers: a repeatability and topographical comparison of choroidal thickness and choroidal vascularity index in healthy eyes. *Transl Vis Sci Technol.* 2020;9(11):8.
23. Agrawal R, Chhablani J, Tan KA, Shah S, Sarvaiya C, Banker A. Choroidal vascularity index in central serous chorioretinopathy. *Retina.* 2016;36(9):1646–1651.
24. Wong RL, Singh SR, Rasheed MA, et al. En-face choroidal vascularity in central serous chorioretinopathy. *Eur J Ophthalmol.* 2020;31(2):536–542.
25. Yang J, Wang E, Yuan M, Chen Y. Three-dimensional choroidal vascularity index in acute central serous chorioretinopathy using swept-source optical coherence tomography. *Graefes Arch Clin Exp Ophthalmol.* 2020;258(2):241–247.
26. Nickla DL, Wallman J. The multifunctional choroid. *Prog Retin Eye Res.* 2010;29(2):144–168.
27. Singh SR, Rasheed MA, Goud A, Sahoo NK, Vupparaboina KK, Chhablani J. Diurnal variation in subfoveal and peripapillary choroidal vascularity index in healthy eyes. *Indian J Ophthalmol.* 2019;67(10):1667–1672.
28. Yun C, Oh J, Han JY, Hwang SY, Moon SW, Huh K. Peripapillary choroidal thickness in central serous chorioretinopathy: is choroid outside the macula also thick? *Retina.* 2015;35(9):1860–1866.
29. Yun C, Oh J, Ahn SE, Hwang SY, Kim SW, Huh K. Peripapillary choroidal thickness in patients with early age-related macular degeneration and reticular pseudodrusen. *Graefes Arch Clin Exp Ophthalmol.* 2016;254(3):427–435.
30. Lee KH, Kim SH, Lee JM, Kang EC, Koh HJ. Peripapillary choroidal thickness change of polypoidal choroidal vasculopathy after anti-vascular endothelial growth factor. *Korean J Ophthalmol.* 2017;31(5):431–438.
31. Kang HM, Kim EW, Choi JH, Koh HJ, Lee SC. Focal lamina cribrosa defects and significant peripapillary choroidal thinning in patients with unilateral branch retinal vein occlusion. *PLoS One.* 2020;15(3):e0230293.
32. Simsek M, Inam O, Sen E, Elgin U. Peripapillary and macular choroidal vascularity index in patients with clinically unilateral pseudoexfoliation syndrome. *Eye (Lond).* 2021;35(6):1712–1720.
33. Song Y, Tham YC, Chong C, et al. Patterns and determinants of choroidal thickness in a multiethnic Asian population: the Singapore epidemiology of eye diseases study. *Ophthalmol Retina.* 2021;5(5):458–467.
34. van Rijssen TJ, van Dijk EHC, Yzer S, et al. Central serous chorioretinopathy: towards an evidence-based treatment guideline. *Prog Retin Eye Res.* 2019;73:100770.
35. Savastano MC, Rispoli M, Lumbroso B. The incidence of neovascularization in central serous chorioretinopathy by optical coherence tomography angiography. *Retina.* 2021;41(2):302–308.
36. Kim YH, Lee B, Kang E, Oh J. Choroidal thickness profile and clinical outcomes in eyes with polypoidal choroidal vasculopathy [published online ahead of print, January 8, 2021]. *Graefes Arch Clin Exp Ophthalmol,* https://doi.org/10.1007/s00417-020-05051-6.
37. Kim YH, Lee B, Kang E, Oh J. Comparison of regional differences in the choroidal thickness between patients with pachychoroid neovasculopathy and classic exudative age-related macular degeneration [published online ahead of print, February 23, 2021]. *Curr Eye Res*, https://doi.org/10.1080/02713683.2021.1887269.
38. Kim YH, Lee B, Kang E, Oh J. Clustering of eyes with age-related macular degeneration or pachychoroid spectrum diseases based on choroidal thickness profile. *Sci Rep*. 2021;11(1):4999.
39. Sonoda S, Sakamoto T, Yamashita T, et al. Choroidal structure in normal eyes and after photodynamic therapy determined by binarization of optical coherence tomographic images. *Invest Ophthalmol Vis Sci.* 2014;55(6):3893–3899.
40. Sonoda S, Sakamoto T, Yamashita T, et al. Luminal and stromal areas of choroid determined by binarization method of optical coherence tomographic images. *Am J Ophthalmol.* 2015;159(6):1123–1131.e1.
41. Lee B, Ahn J, Yun C, Kim SW, Oh J. Variation of retinal and choroidal vasculatures in patients with age-related macular degeneration. *Invest Ophthalmol Vis Sci.* 2018;59(12):5246–5255.
42. Singh SR, Invernizzi A, Rasheed MA, et al. Wide-field choroidal vascular analysis in central serous chorioretinopathy [published online ahead of print, November 2, 2020]. *Eur J Ophthalmol,* https://doi.org/10.1177/1120672120963456.

43. Oh J, Yoo C, Yun CM, Yang KS, Kim SW, Huh K. Simplified method to measure the peripapillary choroidal thickness using three-dimensional optical coherence tomography. *Korean J Ophthalmol.* 2013;27(3):172–177.
44. Wei WB, Xu L, Jonas JB, et al. Subfoveal choroidal thickness: the Beijing eye study. *Ophthalmology.* 2013;120(1):175–180.
45. Suh MH, Park JW, Khandelwal N, Agrawal R. Peripapillary choroidal vascularity index and microstructure of parapapillary atrophy. *Invest Ophthalmol Vis Sci.* 2019;60(12):3768–3775.
46. Tittl M, Maar N, Polska E, Weigert G, Stur M, Schmetterer L. Choroidal hemodynamic changes during isometric exercise in patients with inactive central serous chorioretinopathy. *Invest Ophthalmol Vis Sci.* 2005;46(12):4717–4721.
47. Yun C, Han JY, Cho S, Hwang SY, Kim SW, Oh J. Ocular perfusion pressure and choroidal thickness in central serous chorioretinopathy and pigment epitheliopathy. *Retina.* 2019;39(1):143–149.
48. Ersoz MG, Arf S, Hocaoglu M, Sayman Muslubas I, Karacorlu M. Patient characteristics and risk factors for central serous chorioretinopathy: an analysis of 811 patients. *Br J Ophthalmol.* 2019;103(6):725–729.
49. Daruich A, Matet A, Marchionno L, et al. Acute central serous chorioretinopathy: factors influencing episode duration. *Retina.* 2017;37(10):1905–1915.
50. Mrejen S, Balaratnasingam C, Kaden TR, et al. Long-term visual outcomes and causes of vision loss in chronic central serous chorioretinopathy. *Ophthalmology.* 2019;126(4):576–588.
51. Hanumunthadu D, Matet A, Rasheed MA, Goud A, Vuppurabina KK, Chhablani J. Evaluation of choroidal hyperreflective dots in acute and chronic central serous chorioretinopathy. *Indian J Ophthalmol.* 2019;67(11):1850–1854.
52. Singh SR, Iovino C, Zur D, et al. Central serous chorioretinopathy imaging biomarkers [published online ahead of print, December 7, 2020]. *Br J Ophthalmol,* https://doi.org/10.1136/bjophthalmol-2020-317422.