Original Article

Water-Drinking Test in Central Serous Chorioretinopathy

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Abstract

Purpose: To evaluate choroidal changes in central serous chorioretinopathy (CSCR) patients after water-drinking test (WDT).

Methods: This prospective study included treatment-naïve acute and chronic CSCR eyes and healthy controls. Intraocular pressure and optical coherence tomography measurements with choroidal vascular index (CVI) measurements were done at baseline. Patients were asked to drink 1 L of water, and tests were repeated at 15, 30, and 45 min.

Results: Fifty-six eyes from 42 patients were enrolled. Choroidal area, luminal area, and stromal area were higher at baseline in eyes with acute CSCR compared to healthy controls. Chronic CSCR eyes showed an increase in choroidal area and stromal area and a decrease in the luminal area at 15 min. There was a significant decrease in CVI at 30 and 45 min in chronic CSCR and CVI at 45 min in fellow eyes of acute CSCR. Repeated-measures analysis of variance (ANOVA) showed a significant change in central macular thickness in acute CSCR, choroidal thickness in fellow eyes of acute CSCR, stromal area, and total choroidal area in chronic CSCR. Mixed model ANOVA showed that the change in various choroidal parameters seen had no interaction with the eye type.

Conclusion: Although change in various parameters was seen in acute CSCR, chronic CSCR, and fellow eyes of acute CSCR following WDT, the change was not significantly different among the groups.

Keywords: Central serous chorioretinopathy, Choroidal vascular index, Optical coherence tomography, Water-drinking test

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Introduction

Central serous chorioretinopathy (CSCR) is the fourth most common retinopathy after age-related macular degeneration, diabetic retinopathy, and branch retinal vein occlusion and is characterized by a serous retinal detachment of the macula.[1] It is known to be self-resolving in most of the cases; however, chronic cases may result in an irreversible impairment of visual acuity and contrast sensitivity.[2] CSCR is primarily thought to occur due to hyper-permeability of choroidal vessels in association with retinal pigment epithelium (RPE) dysfunction. This is supported by the increased choroidal thickness seen in CSCR cases compared to healthy eyes.[3] Several studies have reported that choroid in patients with active CSCR is thicker than age-matched healthy eyes.[4]

A recently introduced biomarker, the choroidal vascular index (CVI), has broadened the understanding of this disease.[5] CVI is a ratio of the choroidal luminal area and the total subfoveal choroidal area.[5] To calculate the CVI, a digital segmentation and binarization of the choroid is required to

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separately detect both choroidal stroma and vessels. Agrawal *et al*. demonstrated a higher CVI value in eyes with CSCR compared to healthy controls.[6] Although CVI has a good diagnostic value, the cross-sectional measurements of choroidal thickness and the CVI in itself can have poor prognostic and predictive significances. Considering the fact that most of the patients with CSCR having a poor visual outcome with or without treatment are the ones who present late to the clinic with chronic fluid, educating the patient about the warning symptoms even before the development of disease could be a valuable tool in management. This requires the implementation of diagnostic tools which could detect certain disease-predicting indicators in apparently normal eyes. However, the literature lacks any evidence of such kind of test which could be beneficial in CSCR.

The water-drinking test (WDT) is a provocative test that indirectly evaluates the outflow system of the eye.[7] WDT was previously used as a diagnostic tool for glaucoma; however, it is not widely used due to its poor diagnostic value.[8,9] An increased intraocular pressure (IOP) noticed during the WDT has been attributed to several mechanisms, including elevation of episcleral venous pressure, vitreous hydration, autonomic nervous system stimulation, and more recently, choroidal expansion.[10,11] Kocabeyoglu *et al*. reported that a significant increase in choroidal thickness occurs at 30 and 60 min after WDT in exfoliation syndrome group.[12] This led us to speculate that choroidal stromal and vessel changes may correspond to the increase in choroidal thickness.

In the current study, we aimed to analyze the effect of WDT on different choroidal parameters in acute CSCR, chronic CSCR, non-affected fellow, and healthy eyes.

Methods

This was a prospective, longitudinal interventional study which included 14 eyes of 14 patients with acute CSCR, 14 fellow eyes of acute CSCR patients, 15 chronic CSCR eyes of 15 patients, and 13 eyes of 13 age-matched healthy controls. It was conducted at a tertiary health-care center in South India. Institutional ethics committee approval was obtained and consent to participate was obtained from all subjects prior to the enrollment. The methods adhered to the tenets of the Declaration of Helsinki.

Acute CSCR was defined as the presence of neurosensory retinal detachment (NRD) involving the posterior pole associated with a focal leak or multiple leaks, confirmed by fundus fluorescein angiography, presenting within 4 months from the onset of symptoms. Chronic CSCR or diffuse retinal epitheliopathy was defined as the evidence of RPE decompensation with or without NRD or active leakage sites, confirmed on indocyanine green and fluorescein angiography, presenting with symptoms lasting for 4 months or more.

Inclusion criteria were patients having a diagnosis of treatment-naïve acute or chronic CSCR and age-matched healthy subjects. Exclusion criteria were (i) any ocular surgeries prior to the study; (ii) poor quality of optical coherence tomography (OCT) images; (iii) high myopia defined as a refractive error higher than − 6.00 D (spherical equivalent); (iv) caffeine intake prior to the OCT acquisition; (v) smoking; (vi) axial length higher than 26 mm; and (vii) any evidence of systemic or chorioretinal disease that could interfere with the purpose of the study.

All subjects underwent a full ophthalmological examination including IOP measurement using Goldmann applanation tonometer and OCT. OCT scans were acquired using a Triton swept-source OCT device (Topcon Corporation, Tokyo, Japan), which uses a tunable laser, centered at 1050 nm, able to acquire 100,000 A-scans per second. All scans were performed over a 6 mm × 6 mm area consisting of 256 un-averaged horizontal cross-sectional scans per acquisition. Along with volume scans, a 12 mm horizontal scan was obtained over the fovea.

Subjects were asked to drink 1 L of mineral water within 5 min. Following this, OCT scan and IOP measurements were taken at 15 min, 30 min, and 45 min. An average of three IOP measurements at each time point was taken. All measurements were taken by an experienced examiner (A.G.). The following information was collected from each subject: age, gender, duration of symptoms, refractive error, best corrected visual acuity, IOP, central macular thickness (CMT), height of NRD, and subfoveal choroidal thickness (SFCT). The 12 mm foveal line scans were exported, and the choroid was segmented using previously validated algorithms from our group.[13] The process of CVI calculation included binarization of an OCT scan and automated segmentation of the binarized image.[13,14] The process of segmentation involves steps such as denoising to remove noise from OCT images, localization of RPE for determination of choroid inner boundary, followed by detection of choroid outer boundary. The algorithm calculates the total choroidal area, dark (luminal) area, and bright (stromal) area from the binarized image. The CVI was then calculated by dividing the total dark area by the total choroidal area.

Statistical analysis was performed using the statistical package IBM SPSS v20.0 Statistics for Windows (IBM Corp., Armonk, NY, USA). Descriptive statistics included mean and standard deviation for continuous variables. Wilcoxon signed-rank test was used to assess the changes within the groups from baseline to each time points. Mann–Whitney *U*-test was used to assess the changes between the groups from baseline to each time point. Repeated-measures analysis of variance (ANOVA) was used for "within-group" testing, and mixed model ANOVA was used to test for "within-group" and "between-group" interactions. $P < 0.05$ was considered significant.

Results

A total of 56 eyes of 42 subjects were included: 14 acute CSCR eyes, 15 chronic CSCR eyes, 14 fellow-eyes of patients with acute CSCR, and 13 healthy control eyes. Baseline features of the enrolled subjects are summarized in Table 1, and the trend of OCT parameters after WDT is summarized in Figure 1.

Comparison within groups

Acute central serous chorioretinopathy

A statistically significant increase in CMT by 14.4 ± 19.5 μm (P = 0.016) was seen at 15 min, by 18 ± 20.02 μm (P = 0.005) at 30 min, and by 10 ± 16.8 μm (P = 0.04) at 45 min on comparison with baseline value. The change in the different choroidal parameters was not statistically significant [Table 2]. Repeated-measures ANOVA showed a statistically significant change in CMT (P = 0.005) [Table 3].

Chronic central serous chorioretinopathy

There was a statistically significant increase in total choroidal area at 15 min by 0.18 ± 0.26 mm^2 (P = 0.02) compared to the baseline value. Similarly, there was a statistically significant increase in total choroidal area (0.106 ± 0.16 mm^2, P = 0.02) and stromal area (0.111 ± 0.15 mm^2, P = 0.01), and a decrease in CVI by 0.02 ± 0.03 at 30 min. At 45 min, an increase in the stromal area by 0.074 ± 0.13 mm^2 was the only statistically significant change (P = 0.04). Repeated-measures ANOVA showed a statistically significant change in total choroidal area (P = 0.019) and stromal area (P = 0.019) [Table 3].

Fellow eyes of acute central serous chorioretinopathy

Although not statistically significant, there was an increase in the area of the stromal region, a decrease in the area of the luminal region, and a subsequent decrease of the CVI,

Table 1: Comparison of demographics and baseline clinical characteristics between four groups

Parameter	Acute CSCR	Fellow eye of acute CSCR	Chronic CSCR	Normal subjects
Number of eyes	14	14	15	13
Age (years)	34.92±7.32	34.92±7.32	42.33±5.08	34.46±10.12*
Gender (males)	14	14	15	12
Duration of symptoms	37.78±48 (days)	NA	43.13±38.44 (months)	NA
BCVA (logMAR)	0.15±0.14	0	0.35±0.49	0
Mean CMT (μ)	506.21±190.22	226.85±10.40	275.73±61.73	192.92±20.27
Mean NSD (μ)	324.21±207.23	NA	109±92.07	NA
Mean SFCT (μ)	447.14±99.76	398.35±68.07	468±124.81	354.15±69.86
IOP (mmHg)	14.07±2.55	14.21±3.01	14±2.39	13.53±2.33

*P=0.33. CSCR: Central serous chorioretinopathy, BCVA: Best corrected visual acuity, CMT: Central macular thickness, NSD: Neurosensory detachment, SFCT: Subfoveal choroid thickness, IOP: Intraocular pressure, NA: Not applicable

Table 2: Summary of parameters at baseline, 15, 30, and 45 min after water-drinking test

Group	Parameter	Baseline	15 min	30 min	45 min
Normal	CMT (μ)	192.9±20.3	195.3±20.9 (0.37)	196.2±20.1 (0.32)	193.2±22.5 (0.94)
	SFCT (μ)	354.2±69.9	363.5±69.1 **(0.02)**	366.8±68.4 (0.12)	362.3±74.7 (0.17)
	Choroidal area (mm^2)	2.06±0.49	2.06±0.55 (0.87)	2.07±0.49 (0.71)	2.08±0.55 (0.53)
	Bright area (mm^2)	1.22±0.34	1.23±0.37 (0.75)	1.22±0.31 (0.99)	1.21±0.37 (0.81)
	Luminal area (mm^2)	0.83±0.19	0.83±0.22 (0.89)	0.85±0.20 (0.37)	0.86±0.21 **(0.04)**
	CVI	0.41±0.04	0.41±0.04 (0.76)	0.41±0.03 (0.59)	0.42±0.04 (0.10)
Acute CSCR	CMT (μ)	506.2±190.2	520.6±202.0 **(0.016)**	524.2±201.1 **(0.005)**	516.2±193.7 **(0.04)**
	SFCT (μ)	447.1±99.8	444.5±95.0 (0.42)	424.4±102.5 (0.28)	422.9±92.1 (0.23)
	Choroidal area (mm^2)	2.53±0.54	2.56±0.53 (0.61)	2.56±0.53 (0.33)	2.55±0.56 (0.71)
	Bright area (mm^2)	1.51±0.36	1.54±0.34 (0.61)	1.55±0.35 (0.19)	1.54±0.34 (0.46)
	Luminal area (mm^2)	1.02±0.21	1.02±0.22 (0.75)	1.01±0.21 (0.76)	1.00±0.23 (0.45)
	CVI	0.41±0.04	0.40±0.03 (0.59)	0.39±0.03 (0.24)	0.39±0.02 (0.16)
Fellow eyes of acute CSCR	CMT (μ)	226.9±10.4	230.8±10.8 **(0.0002)**	230.0±10.7 **(0.0002)**	230.9±12.6 **(0.0002)**
	SFCT (μ)	398.4±68.1	410.5±78.6 (0.05)	401.4±77.2 (0.67)	399.5±83.7 (0.88)
	Choroidal area (mm^2)	2.35±0.54	2.40±0.48 (0.11)	2.39±0.45 (0.37)	2.39±0.46 (0.49)
	Bright area (mm^2)	1.37±0.29	1.42±0.28 (0.09)	1.42±0.35 (0.23)	1.44±0.29 (0.15)
	Luminal area (mm^2)	0.98±0.21	0.98±0.25 (0.98)	0.97±0.21 (0.82)	0.95±0.23 (0.27)
	CVI	0.42±0.37	0.41±0.04 (0.28)	0.41±0.05 (0.20)	0.39±0.05 (0.05)
Chronic CSCR	CMT (μ)	275.7±61.7	279.1±63.9 (0.25)	277.3±66.3 (0.70)	276.7±66.8 (0.85)
	SFCT (μ)	462.6±89.3	458.2±92.9 (0.55)	455.9±97.4 (0.37)	461.2±93.1 (0.83)
	Choroidal area (mm^2)	2.70±0.62	2.88±0.55 **(0.02)**	2.81±0.56 **(0.02)**	2.77±0.60 (0.17)
	Bright area (mm^2)	1.58±0.38	1.71±0.33 **(0.02)**	1.69±0.35 **(0.01)**	1.65±0.38 **(0.04)**
	Luminal area (mm^2)	1.21±0.27	1.17±0.27 (0.16)	1.12±0.26 (0.82)	1.12±0.25 (0.99)
	CVI	0.42±0.37	0.41±0.05 (0.29)	0.40±0.04 **(0.045)**	0.40±0.04 (0.09)

Values in bracket in each cell represent the P values of Wilcoxon signed-rank test for each cell variable tested against its corresponding baseline variable. CSCR: Central serous chorioretinopathy, CMT: Central macular thickness, SFCT: Subfoveal choroid thickness, CVI: Choroidal vascular index. Numbers in bold represent significant P values

Table 3: Summary of results of the mixed model analysis of variance, for within- and between-group comparisons

Variables	Overall "within-groups" effects (normal, acute CSCR, fellow eye of acute CSCR, chronic CSCR)	Overall "between - groups" effects	Interaction with group
CMT	**0.002** (0.668, **0.005**, 0.151, 0.774)*	**<0.001**	0.145
SFCT	0.613 (0.111, 0.290, **0.001**, 0.646)*	**<0.001**	0.163
Choroidal area	**0.034** (0.882, 0.798, 0.564, **0.019**)*	**0.005**	0.434
Bright	**0.015** (0.940, 0.697, 0.278, **0.019**)*	**0.007**	0.408
Dark area	0.377 (0.259, 0.771, 0.470, 0.128)*	**0.014**	0.294
CVI	0.064 (0.272, 0.458, 0.105, 0.112)*	0.869	0.219

Values inside cells are *P* values; significant values are depicted in bold letters. *Values in brackets signify *P* values of change in parameters across the time frame in normal, acute CSCR, fellow eyes of acute CSCR and chronic CSCR, respectively. CSCR: Central serous chorioretinopathy, CMT: Central macular thickness, SFCT: Subfoveal choroid thickness, CVI: Choroidal vascular index

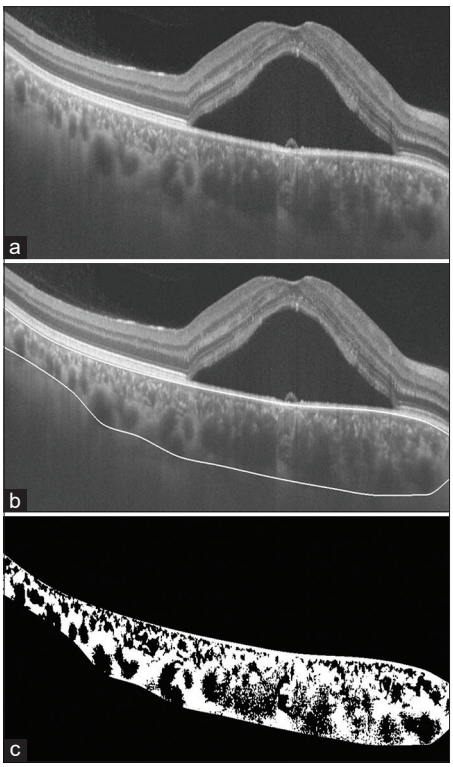

Figure 1: Example of automated choroid segmentation and binarization. (a) Original optical coherence tomography of a case of acute central serous chorioretinopathy. (b) Segmentation of the choroidal boundaries. (c) The binarized output obtained from software

especially evident at 45 min. Repeated-measures ANOVA showed a statistically significant change in SFCT ($P = 0.001$).

Healthy control eyes

A statistically significant ($P = 0.04$) increase in the total luminal area by 0.025 ± 0.04 mm^2 was seen at 45 min. Although not statistically significant, an increase in the total luminal area of 0.015 ± 0.06 mm^2 was seen at 30 min. The CVI showed an increasing trend.

A summary of the parameters is shown in Table 2 and Figure 2.

Comparison between groups after water-drinking test

1. Acute CSCR versus fellow eye of acute CSCR
   The baseline and 15 min change in SFCT ($P = 0.000$ and $P = 0.032$, respectively) and change in CMT at 30 min ($P = 0.011$) were significantly higher in acute CSCR eyes.
2. Acute CSCR versus chronic CSCR
   Significantly higher CMT and neurosensory detachment were found at baseline ($P = 0.000$ and $P = 0.001$, respectively) in acute CSCR. At 30 min, a higher CMT increase was noticed in acute CSCR ($P = 0.018$).
3. Healthy eyes versus acute CSCR
   At baseline, significantly higher CMT and SFCT values were noticed in acute CSCR ($P = 0.000$ and 0.001). Similarly, a significantly higher increase in choroidal area, luminal area, and stromal area was found in acute CSCR ($P = 0.027$, 0.045 and 0.026, respectively). However, there was an increase in CVI at 45 min in normal eyes as compared to acute CSCR ($P = 0.038$).
4. Healthy eyes versus fellow eyes of acute CSCR
   There was a decrease in CVI in fellow eyes of acute CSCR at 45 min as compared to an increased value in normal eyes ($P = 0.016$).
5. Healthy eyes versus chronic CSCR
   Baseline choroidal area, stromal area, and luminal area ($P = 0.006$, 0.015, and 0.004, respectively) were significantly higher in eyes with chronic CSCR. Similarly, a significantly higher increase in the choroidal area and stromal area and decrease in the luminal area were noted in eyes with chronic CSCR, as compared to healthy eyes, at 15 min ($P = 0.032$, 0.044, and 0.039, respectively). There was an increase in CVI at 30 and 45 min in normal eyes as compared to chronic CSCR eyes ($P = 0.048$ and 0.022, respectively).
6. Fellow eye of acute CSCR versus chronic CSCR.

Baseline CMT and SFCT were higher in chronic CSCR eyes than fellow eyes of acute CSCR ($P < 0.001$ for each). Change in IOP was not found to be significant after WDT in all groups at all the time points. No significant correlation was seen between the IOP measurements and OCT parameters.

Mixed model analysis of variance

The "within-group" analysis of the model shows the significance of change in a variable over time, in the overall cohort, along with the significance of change in the variable

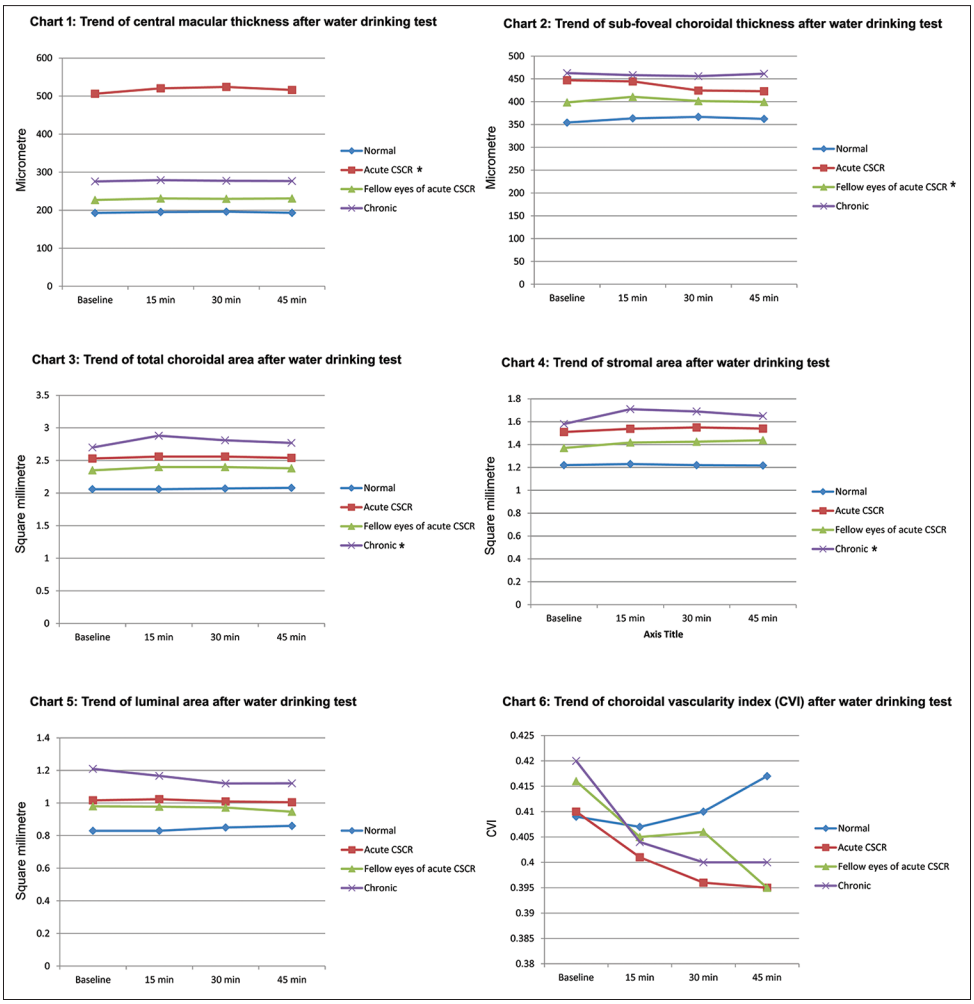

Figure 2: Trend of various parameters after water-drinking test (significant parameters have been marked with an asterisk)

in each group separately. Table 3 shows that the change in CMT (P = 0.002), choroidal area (P = 0.034), and bright area (P = 0.015), over time, was significant in the overall cohort, while SFCT, dark area, and CVI were not significant. However, on individual group *post hoc* analysis, it was seen that the significance seen in CMT was due to the change in acute CSCR (0.005). Similarly, the significance seen in the choroidal area and bright area was due to changes in the chronic CSCR group (P = 0.019 in both variables). Interestingly, although the change in SFCT was not significant in the overall cohort, significance was seen in fellow eyes of acute CSCR (P = 0.001). The "between-group" analysis shows whether the values of each variable were significantly different from the other groups at all the time points. There was a significant difference with respect to CMT, SFCT, total choroidal area, luminal area, and stromal area, but not CVI. As this significance can be affected by the significant difference in the baseline parameters in the groups, an interaction with the group was examined. No statistically significant interaction was seen between the changes in the variables (CMT, SFCT, total choroidal area, luminal area, stromal area, and CVI) and the type of eye (normal, acute CSCR, fellow eye of acute CSCR, and chronic CSCR), suggesting that the changes that were seen in within-group analysis were not significantly different from other groups [Table 3].

Discussion

In our study, significant changes in choroidal parameters, after WDT, were noticed in eyes with chronic CSCR. Although higher at baseline, CVI in acute, chronic, and fellow eyes of acute CSCR was found to be lower at 15, 30, and 45 min compared to normal eyes, respectively. However, no statistically significant effect of the type of eye at baseline was seen on the response to WDT.

We used a previously described choroidal binarization technique to separately assess the choroidal vasculature and the stromal area to determine potential changes in each segment of the choroid.[13] We found a statistically significant increase in the total choroidal area and the stromal area after WDT at 30 min and stromal area after 45 min in chronic CSCR eyes. Chronic increase of choroidal permeability in CSCR may be accentuated during WDT. This phenomenon determines an augmented protein accumulation in the stroma and an increased

extravascular oncotic pressure. This may explain the increase in stromal area in chronic CSCR.

A similar phenomenon was seen in acute CSCR eyes and in fellow eyes of acute CSCR patients where a non-significant decrease in the luminal region and increase in the bright region were seen. On the other hand, in healthy eyes, an increase in the area of the luminal region was seen along with a minimal increase in the stromal area and the total choroidal area. This could have been due to the fact that the choroidal vessels in healthy eyes are not hyper-permeable, and this might have resulted in the compartmentalization of the fluid within the vessels with minimal egress, unlike eyes with CSCR.

Agrawal *et al*. demonstrated that CVI is seen to be higher in eyes with CSCR than in healthy eyes.[6] Similar results were found in our study while comparing the baseline choroidal parameters, as shown in Table 1. However, the increase in the choroidal stromal area and the decrease in the choroidal vessel area after WDT resulted in a decrease in the CVI value in eyes with acute CSCR, fellow eyes of acute CSCR eyes, and eyes with chronic CSCR. On the other hand, the increase in the choroidal vessel area in the healthy eyes resulted in the increase in the CVI values after WDT. This observation can be instrumental in detecting eyes that are prone to develop CSCR. Eyes predisposed to develop CSCR may have the tendency towards a decrease in CVI, i.e., minimal increase in the vessel are compared to the stromal area. Conversely, eyes that are not predisposed to develop CSCR may develop an increase in CVI after WDT, akin to healthy eyes. However, results of the mixed model ANOVA showed that although there was a significant change in the SFCT in fellow eyes of acute CSCR, total choroidal area, and stromal area of chronic CSCR, there was no significant interaction between the type of eye and the OCT parameters. This implies that the changes seen in the OCT parameters after WDT in the different groups were not significantly different when compared to other groups. On the other hand, there were significant "between-group" differences for every OCT parameter, suggesting a significant variation in the baseline values among the groups. Thus, the results of WDT in pachychoroid eyes did not appear to be significantly different from normal eyes, although it requires further validation with a larger sample size. Apart from this, there are other limitations to the study. The manual measurements taken in the study are subject to variability due to intra-observer variation. Furthermore, if the scans do not pass through the same point before and after the test, this could have introduced bias owing to the fact that changes seen after WDT are minimal. Second, diurnal variations in the various choroidal parameters have been seen in pachychoroid spectrum of diseases and even in normal eyes, and this could have influenced the results of the study.[15,16]

In conclusion, WDT resulted in an increase in choroidal stromal area and the total choroidal area and a decrease in CVI in eyes with acute CSCR, chronic CSCR, and fellow eyes of acute CSCR. On the other hand, it resulted in an increase in choroidal vessel caliber, along with an increase in CVI in normal eyes. Although we did not find these changes to be significantly different on comparing with other groups, with the help of further studies with a larger sample size, this test could possibly help in predicting eyes that are predisposed to develop CSCR.

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Conflicts of interest

There are no conflicts of interest.

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