Submacular and Peripapillary Choroidal Vascularity Index in Chronic Central Serous Chorioretinopathy

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ABSTRACT

Purpose: In this study, it was aimed to evaluate the submacular and peripapillary choroidal vascularity index (CVI) in treatment-naive patients with chronic central serous chorioretinopathy (CSCR).

Material and Method: This cross-sectional study included patients with unilateral chronic CSCR and age- and sex-matched healthy controls. Subfoveal and peripapillary choroidal thickness (CT) were measured from EDI-OCT images in all participants. The CSCR eyes of the patients with CSCR were assigned into group 1 while healthy eyes of the patients with CSCR into group 2 and the right eyes of healthy controls into group 3. CVI was calculated as the ratio of luminal area to total choroidal area after EDI-OCT images processed using binarization method. The stromal area was calculated by subtracting the luminal area from the total choroidal area.

Results: The study included 18 patients with chronic CSCR and 19 controls. There was no significant difference in mean subfoveal CT, peripapillary CT and CVI values between group 1 and group 2. It was found that subfoveal CT and peripapillary CT values were significantly higher in group 1 and group 2 while peripapillary CVI values were significantly higher in group 1 when group 3. While no significant difference was observed between the submacular CVI values among groups 1, 2 and 3, luminal area and stromal area values were significantly higher in group 1 when compared to groups 2 and 3.

Conclusion: Chronic CSCR can cause both increased vascularization and fluid retention in the stroma in the submacular area. Although this may increase the subfoveal CT, it may not change the submacular CVI values. In the peripapillary choroid, on the other hand, it seems that the luminal area is mainly affected, and the ratio of the increased luminal area to the unaffected stromal area may be explanatory for the high peripapillary CVI.

Keywords: Central serous chorioretinopathy, Choroidal thickness, Choroidal vascularity index, Chronic, EDI-OCT.

INTRODUCTION

Central serous chorioretinopathy (CSCR) is the most frequently diagnosed entity among pachychoroid disorders, which is characterized by serous retinal detachment at macular region of middle-aged individuals. Serous retinal detachment may be accompanied by serous retinal pigment epithelium (RPE) detachment. Although acute CSCR can be resolved spontaneously within a few months, natural course generally includes recurrent attacks or progression to chronic disease.[1,2] Chronic CSCR is defined as presence of retinal fluid for at least 3-6 months. The chronic CSCR can lead loss of vision due to persistent serous retinal detachment.[3,4]

Although etiology or pathogenesis hasn't been fully elucidated in acute CSCR, it is though that subretinal fluid results from choroidal vascularity with increased permeability. It has been proposed that diffuse RPE decompensation impairs subretinal fluid absorption in chronic CSCR and that impaired and thickened choroidal tissue leads permanent disruption in choroidal permeability and continuous fluid flow.[5]

Regardless of CSCR stage, increased choroidal thickness is the most typical finding in CSCR.[6] Choroidal thickness (CT) can be quantitatively assessed after introduction of enhanced depth imaging-optical coherence tomography (EDI-OCT) into routine practice. It is thought that increased CT results from abnormal choroidal circulation and increased vascular permeability. In recent years, choroidal

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vascularity index (CVI), determined by processing EDI-OCT images using binarization method, has emerged as a more reliable biomarker than CT in many ocular and systemic diseases involving choroid.[7-14] CVI provides quantitative values for vascular and stromal structures in the choroid which is definitive enough to compare with histopathology.

In studies on CVI in CSCR, it was reported that CVI values were higher in CSCR eye when compared to other eye.[13,14] Although CSCR-related choroidal changes were mostly studied at submacular area, there are studies reporting increased choroidal thickness at peripapillary area.[15] In this study, we aimed to compare submacular and peripapillary CVI values from CSCR patients with data obtained from healthy contralateral eyes and healthy subjects.

MATERIALS AND METHODS

This cross-sectional study was conducted between March, 2020 and December, 2020. The study included patients with unilateral chronic CSCR and age- and sex-matched healthy controls. All subjects gave written informed consent before study participation. The study was approved by Ethics Committee of Ankara Teaching and Research Hospital (approval#526). It was conducted in accordance to tenets of Helsinki Declaration.

The CSCR eyes of the patients with CSCR were assigned into group 1 while healthy eyes of the patients with CSCR into group 2 and the right eyes of healthy controls into group 3. Due to population preponderance in healthy controls, only measurements from right eyes were included to the analyses. The diagnosis of CSCR was made in the presence of subfoveal fluid for at least 3 months on OCT. The patients with CSCR in one eye were included to the study.

Exclusion criteria included bilateral CSCR (only for patients with CSCR), high myopia, history of vitreoretinal surgery, uveitis, diabetic retinopathy and retinal vascular occlusions. Patients with poor quality OCT images were excluded.

All subjects underwent a comprehensive ophthalmological examination including best-corrected visual acuity (BCVA) assessment by Snellen chart, intraocular pressure measurement, biomicroscopic anterior segment examination, dilated fundus examination, fluorescein angiography, OCT, EDI-OCT and axial length measurement (IOLMasterTM; Carl Zeiss Meditec, Jena, Germany).

Choroidal image analysis

In all subjects, EDI-OCT images (Heidelberg Engineering GmbH, Heidelberg, Germany) were used for CT and CVI measurements. Subfoveal CT was manually measured as the distance outer margin of RPE to inner scleral margin. Peripapillary CT was calculated separately for nasal, temporal, superior and inferior quadrant from images obtained with vertical and horizontal scans involving

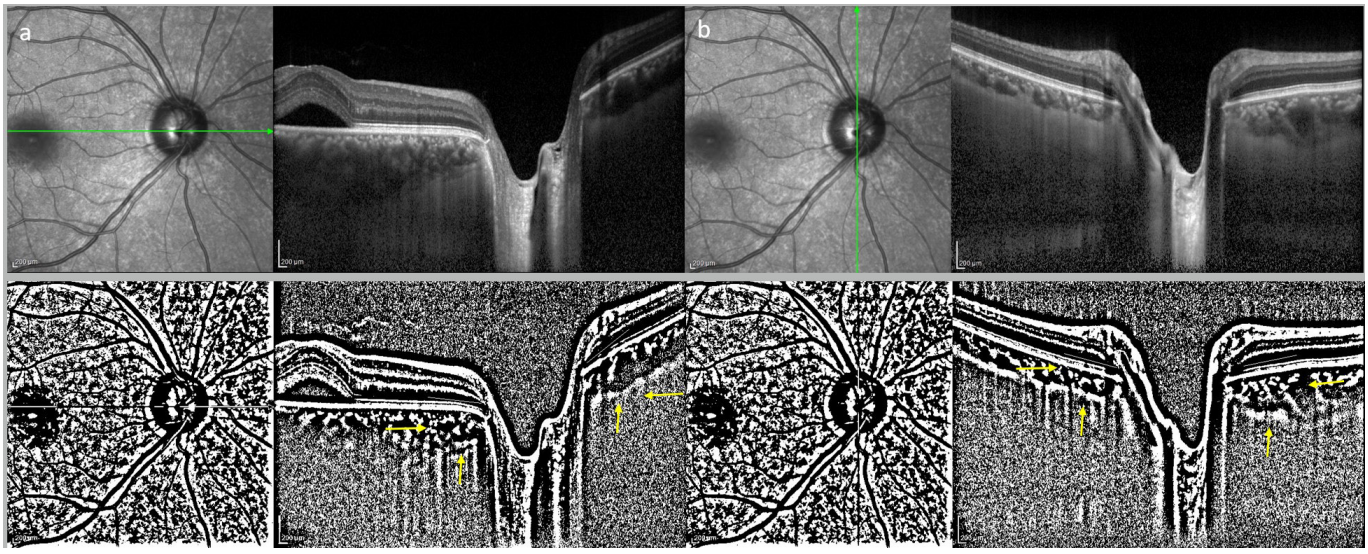

Figure 1: *Peripapillary choroidal vascularity index measurement using ImageJ software (https://imagej.net).* **a)** *horizontal (temporal and naSal) and* **b)** *vertical (superior and inferior) EDİ-OCT scans were performed by using optic nerve head as center. Scans were binarized using Niblack auto tresholding technique. A line (1000 µm in width) was drawn; then, peripapillary choroidal areas (yellow arrows) were selected using polygon option. Upper margin corresponded to retinal pigment epithelium while inferior margin corresponded to scleral junction.*

the area 1000 µm distance from optic nerve margin in manual manner. To exclude diurnal changes in CT, all measurements were performed between 09:00 AM and 11:00 AM.

For CVI measurements, binarization of EDI-OCT images was used as described by Agrawal et al.[8] The Niblack auto local thresholding technique was used to determine border of luminal (vascular) area and stromal area. Then, images were transformed into RGB image and luminal area was determined using color thresholding tool. CVI was calculated as the ratio of luminal area (LA) to total choroidal area (TCA). Submacular CVI was measured on EDI-OCT section with a central area of 1500 µm. Peripapillary CT was calculated separately for nasal, temporal, superior and inferior quadrant from images obtained with vertical and horizontal scans involving the area 1000 µm distance from optic nerve margin. The stromal area (SA) was calculated by subtracting the luminal area from TCA. In addition, LA ratio to SA was calculated as LSR parameter. All measurements were performed by two researcher (BSG, AG).

Statistical analysis

Data were analyzed using SPSS version 17.0 (IBM Corporation, Armonk, NY, USA). Numerical variables are presented as mean ± standard deviation while categorical variables are presented as count (percent). The normality of numerical variables was assessed using Kolmogorv-Smirnov test. Categorical variables were compared using Chi-square test. Dependent t test was used to compare group 1 and 2 while independent samples t test was used to compare group 3 with group 1 or 2. Multivariate logistic regression analysis was performed to adjust potential effects of axial length on CT. A p value <0.05 was considered as statistically significant.

FINDINGS

The study included 18 patients with chronic CSCR and 19 controls. Mean age was 42.1±9.5 (25-56) years in the CSCR group and 40.2 ± 3.2 (27-55) years in the control group (p>0.05). Of the patients with CSCR, 66.6% were male while 63.1% of controls were male (p>0.05). No significant differences were detected regarding refractive error (1.52 ±0.95 SE, 1.86 ± 0.97 SE and 1.74 ± 1.06 SE, respectively), intraocular pressure (14.2 ± 3.3 mmHg, 14.1 ± 2.9 mmHg and 13.9± 1.9 mmHg, respectively) and axial length (23.18 ± 0.72 mm, 23.38 ± 0.49 mm and 23.45± 0.64 mm, respectively) among groups 1, 2 and 3 (p>0.05, for all).

It was found that mean subfoveal CT (µm) was 449.60±105.73 in group 1, 449.33±100.02 in group 2 and 381.41±80.91 in group 3. Mean pCT (µm) was calculated as 336.07±107.90 in group 1, 326.93±95.27 in group 2 and 266.64±80.35 in group 3 for temporal quadrant; 310.73±118.55 in group, 309.73±89.52 in group 2 and 262.64±118.10 in group 3 for nasal quadrant; 333.80±121.76 in group 1, 339.87±130.91 in group 2 and 246.29±90.10 in group 3 for superior quadrant; and 230.20±81.59 in group 1, 239.20±100.86 in group 2 and 210.71±104.20 in group 3 for inferior quadrant. It was found that there was no significant difference in sCT and pCT between group 1 and 2 (p>0.05, for all) while it was higher in group 1 and 2 when compared to group 3 (p<0.05, for all) (Table 1)

When choroidal vascular parameters were assessed, mean subfoveal CVI (%) was 62.15±3.06 in group 1, 63.42±2.78 in group 2 and 64.01±2.54 in group 3. No significant

Table 1: *Subfoveal ve peripapillary choroidal thickness values in groups*

	Group 1 Mean±SD	Group 2 Mean ±SD	Group 3 Mean ±SD	p value
sCT (µm)	449.60±105.73	449.33±100.02	381.41±80.91	0.990[a], **0.048[b]**, **0.042[c]**
pCT (µm)				
Temporal	336.07±107.90	326.93±95.27	266.64±80.35	0.485[a], **0.005[b], 0.006[c]**
Nasal	310.73±118.55	309.73±89.52	262.64±118.10	0.963[a], **0.045[b], 0.048[c]**
Superior	333.80±121.76	339.87±130.91	246.29±90.10	0.808[a], **0.039[b], 0.033[c]**
Inferior	230.20±81.59	239.20±100.86	210.71±104.20	0.668[a], **0.048[b], 0.042[c]**

Bold values are statistically significant. SD: Standard deviation; sCT: Subfoveal choroidal thickness; pCT: Peripapillary choroidal thickness

[a] Comparison of group 1 and group 2 (Dependent t-test)

[b] Comparison of group 1 and group 3 (Independent t-test)

[c] Comparison of group 1 and group 2 (Independent t-test)

difference was observed in subfoveal CVI among ($p>0.05$, for all) while subfoveal TCA, LA and SA values were significantly higher in group 1 when compared to group 3 ($p<0.05$, for all). Mean peripapillary CVI (%) values for temporal, nasal, superior and inferior quadrants were 64.50±2.99, 62.88±3.25, 64.16±3.82 and 64.06±3.46 in group while 63.94±3.59, 61.95±3.13, 62.68±2.95 and 63.07±2.85 in group 2 and 62.21±3.52, 59.29±5.61, 61.98±3.32 and 61.44±4.76 in group 3, respectively. Peripapillary CVI values were significantly higher in all

Table 2: *Submacular and peripapillary choroidal vascular values*

	Group 1 Mean ±SD	Group 2 Mean ±SD	Gr0up 3 Mean ±SD	p value
Submacular				
TCA (mm^2)	1.82±0.39	1.73±0.36	1.52±0.23	0.697[a], **0.014[b], 0.004[c]**
LA (mm^2)	1.13±0.22	1.05±0.20	0.97±0.15	**0.045[a]**, **0.031[b],** 0.132[c]
SA (mm^2)	0.69±0.18	0.60±0.17	0.55±0.09	**0.039[a]**, **0.008[b],** 0.201[c]
CVI (%)	62.15±3.06	63.42±2.78	64.01±2.54	0.098[a], 0.069[b], 0.532[c]
LSO	1.65±0.21	1.74±0.21	1.79±0.20	0.099[a], 0.076[b], 0.557[c]
Peripapillary				
Temporal				
TCA (mm^2)	0.72±0.15	0.72±0.14	0.62±0.13	0.565[a], 0.067[b], 0.058[c]
LA (mm^2)	0.46±0.09	0.45±0.10	0.39±0.10	0.615[a], 0.050[b], 0.054[c]
SA (mm^2)	0.25±0.05	0.24±0.04	0.23±0.03	0.528[a], 0.180[b], 0.155[c]
CVİ (%)	64.50±2.99	63.94±3.59	62.21±3.52	0.429[a], **0.045[b],** 0.202[c]
LSR	1.83±0.25	1.80±0.30	1.66±0.25	0.553[a], 0.085[b], 0.215[c]
Nasal				
TCA (mm^2)	0.67±0.15	0.66±0.14	0.58±0.11	0.942[a], 0.081[b], 0.081[c]
LA (mm^2)	0.42±0.11	0.41±0.10	0.34±0.09	0.759[a], 0.056[b], 0.079[c]
SA (mm^2)	0.24±0.05	0.25±0.05	0.23±0.03	0.751[a], 0.338[b], 0.195[c]
CVI (%)	62.88±3.25	61.95±3.13	59.29±5.61	0.192[a], **0.043[b]**, 0.124[c]
LSR	1.71±0.23	1.64±0.23	1.50±0.39	0.192[a], 0.094[b], 0.249[c]
Superior				
TCA (mm^2)	0.73±0.19	0.74±0.18	0.62±0.12	0.473[a], 0.097[b], 0.068[c]
LA (mm^2)	0.47±0.14	0.47±0.12	0.38±0.08	0.837[a], 0.074[b], 0.054[c]
SA (mm^2)	0.25±0.06	0.26±0.06	0.23±0.04	0.142[a], 0.251[b], 0.062[c]
CVI (%)	64.16±3.82	62.68±2.95	61.98±3.32	0.151[a], **0.043[b]**, 0.556[c]
LSR	1.81±0.29	1.69±0.20	1.65±0.25	0.085[a], 0.112[b], 0.617[c]
Inferior				
TCA (mm^2)	0.64±0.17	0.65±0.16	0.52±0.15	0.793[a], 0.052[b], **0.031[c]**
LA (mm^2)	0.41±0.12	0.41±0.11	0.32±0.10	0.956[a], 0.068[b], 0.061[c]
SA (mm^2)	0.23±0.05	0.22±0.05	0.19±0.05	0.406[a], **0.040[b],** 0.098[c]
CVI (%)	64.06±3.46	63.07±2.85	61.44±4.76	0.262[a], **0.044[b]**, 0.122[c]
LSR	1.78±0.23	1.70±0.19	1.63±0.32	0.694[a], 0.262[b], 0.382[c]

Bold values are statistically significant. SD: Standard deviation; TCA: Total choroid area, LA: Luminal area, SA: Stromal area; CVI: Choroidal vascularity index LSR: Luminal/stromal ratio.

[a] Comparison of group 1 and group 2 (Dependent t-test),

[b] Comparison of group 1 and group 3 (Independent t-test),

[c] Comparison of group 1 and group 2 (Independent t-test)

quadrants in group 3 when compared to those in group 3 ($p<0.05$, for all) (Table 2).

DISCUSSION

Based on our findings, there are no significant differences in subfoveal CT, peripapillary CT, submacular CT, submacular CVI and peripapillary CVI between CSCR eyes and other eyes of patients with chronic CSCR. However, subfoveal CT and peripapillary CT values were significantly higher in CSCR eyes and other eyes of patients with chronic CSCR when compared to eyes of healthy controls. In addition, CVI values were significantly higher in CSCR eyes when compared to eyes of healthy controls. Although there was no significant difference in submacular CVI values among groups, both vascular area and stromal area values were found to be significantly higher in CSCR eyes when compared to group 2 and group 3. These findings suggest that chronic CSCR can lead an increase in both vascularization in submacular area and stromal area due to chronic fluid retention and that vascular area is the primary component involved in the peripapillary area.

The CSCR is a disease characterized by increased choroidal thickness and fluid leakage from dilated choroidal vessels with high permeability into stromal area. In the CSCR, typical finding is serous retinal detachment. Although pathogenesis is unclear, exogenous and endogenous hypercortisolism is the most commonly implied risk factor.[16,17] The choroid can provide auto-regulation of blood flow by nitric oxide and prostaglandin production.[18,19] It was shown that increased cortisol level leads epinephrine release; and, thus, influences on nitric oxide, prostaglandins and free oxygen radicals production, resulting in vasodilatation and increased permeability in choroidal vessels.[20]

The CSCR is the most commonly studied biomarker of EDI-OCT. In many studies, increased CT was shown at macular region in both CSCR and health eyes in acute and chronic CSCR.[21-24] In addition, the CT was decreased by resorption of fluid either spontaneously or with treatment.[25] In the limited number of studies evaluating peripapillary CT in CSCR, it was shown that increased CT isn't limited to macular region and involves whole choroid in CSCR.[15,26] In agreement with literature, it was shown that both subfoveal and peripapillary CT values were higher in eyes with chronic CSCR when compared to healthy controls.

CVI is another biomarker obtained from EDI-OCT images, which provides more reliable and definitive results. It has been used in the diagnosis and follow-up of many ophthalmological and systemic disease in recent years.[7-14] The CT shows total thickness of vascular and stromal tissues but not allows assess these tissues separately. In other words, it addresses CT as a single component; thus, it is possible to overlook increased stromal tissue against decreased vascular tissue in the choroid with normal thickness. CVI provides a ratio of vascular area to total area and allows assessment of choroidal components separately. In studies on acute CSCR, it was reported that vascular area was increased relatively to stromal area in CSCR eyes, resulting significantly higher CVI when compared to other eyes of patients and healthy controls.[13-14] Kim et al. reported that subfoveal CVI was comparable to normal controls in chronic CSCR.[27] As similarly, no significant difference was observed in submacular CVI values between patients with chronic CSCR and healthy controls. However, a significant increase was found in both vascularization and stromal area in submacular area in chronic CSCR. In chronic CSCR, stromal vascularization surrounding vascular network together with increased permeability presumably lead chronic edema and submacular CVI values within normal range although both components are increased.

When peripapillary CVI values were assessed in our study, it was found that all values measured from 4 quadrants were higher in eyes with chronic CSCR when compared to healthy controls. This finding showed that choroidal changes in chronic CSCR aren't only limited to macular area but also involve peripapillary area. However, both vascular and stromal areas are affected in submacular region while vascular area is primarily affected in peripapillary region in chronic phase.

This study has some limitations including limited sample size and borderline statistical significance in our results. Thus, our results should be supported by comprehensive, prospective studies.

In conclusion, our results showed that chronic CSCR can lead both increased vascularization in submacular region and fluid retention in stroma in chronic CSCR. Although this causes increase in subfoveal, it may not change CVI values. It can be seen that vascular area is primarily affected in peripapillary choroid; the ratio of increased vascular area: stromal area ratio can explain high peripapillary CVI values.

REFERENCES

1. Arvas S. Santral seröz koryoretinopati. Ret-Vit 2011;19:75-8.
2. 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.
3. Gelişken Ö, Yılmaz S, Kaderli B. Kronik santral seröz koryoretinopati. Ret-Vit 2007;15:1-6.

4. Hanumunthadu D, Tan ACS, Singh SR, et al. Management of chronic central serous chorioretinopathy. Indian J Ophthalmol 2018;66:1704-14.
5. Mudvari SS, Goff MJ, FuAD, et al. The natural history of pigment epithelial detachment associated with central serous chorioretinopathy. Retina 2007;27:1168-73.
6. Nkrumah G, Paez-Escamilla M, Singh SR, et al. Biomarkers for central serous chorioretinopathy. Ther Adv Ophthalmol 2020;12:2515841420950846.
7. Agrawal R, Gupta P, Tan KA, et al. 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.
8. 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 11 2016:e0146344.
9. Keenan TD, Klein B, Agrón E, et al. Choroidal thickness and vascularity vary with disease severity and subretinal drusenoid deposit presence in nonadvanced age-related macular degeneration. Retina 2020;40:632-42.
10. 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;255:935-43.
11. Aribas YK, Hondur AM, Tezel TH. Choroidal vascularity index and choriocapillary changes in retinal vein occlusions. Graefes Arch Clin Exp Ophthalmol 2020;258:2389-97.
12. Kim M, Ha MJ, Choi SY, et al. Choroidal vascularity index in type-2 diabetes analyzed by swept-source optical coherence tomography. Sci Rep 2018;8:70.
13. Agrawal R, Chhablani J, Tan K-A, et al. Choroidal vascularity index in central serous chorioretinopathy. Retina 2016;36:1646-51.
14. Rasheed MA, Goud A, Mohamed A, et al. Change in choroidal vascularity in acute central serous chorioretinopathy. Indian J Ophthalmol 2018;66:530-4.
15. Yun C, Oh J, Han JY, et al. Peripapillary choroidal thickness in central serous chorioretinopathy: Is choroid outside the macula also thick? Retina 2015;35:1860-6.
16. Garg SP, Dada T, Talwar D, et al. Endogenous cortisol profile in patients with central serous chorioretinopathy. Br J Physiol Opt 1997;81:962-4.
17. Haimovici R, Rumelt S, Melby J. Endocrine abnormalities in patients with central serous chorioretinopathy. Ophthalmology 2003;110:698-703.
18. Deussen A, Sonntag M and Vogel R. L-arginine derived nitric oxide: a major determinant of uveal blood flow. Exp Eye Res 1993;57:129-34.
19. Hardy P, Nuyt AM, Abran D, et al. Nitric oxide in retinal and choroidal blood flow autoregulation in newborn pigs: interactions with prostaglandins. Pediatr Res 1996;39:487-93.
20. Tittl MK, Spaide RF, Wong D, et al. Systemic findings associated with central serous chorioretinopathy. Am J Ophthalmol 1999;128:63-8.
21. Imamura Y, Fujiwara T, Margolis R, et al. Enhanced depth imaging optical coherence tomography of the choroid in central serous chorioretinopathy. Retina 2009;29:1469-73.
22. Kim SW, Oh J, Kwon SS, et al. 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;31:1904-11.
23. Maruko I, Iida T, Sugano Y, et al. Subfoveal choroidal thickness in fellow eyes of patients with central serous chorioretinopathy. Retina 2011;31:1603-8.
24. Spaide RF, Ryan EH Jr. Loculation of fluid in the posterior choroid in eyes with central serous chorioretinopathy. Am J Ophthalmol 2015;160:1211-6.
25. Kang NH, Kim YT. Change in subfoveal choroidal thickness in central serous chorioretinopathy following spontaneous resolution and low-fluence photodynamic therapy. Eye 2013;27:387-91.
26. Singh SR, Invernizzi A, Rasheed MA, et al. Wide-field choroidal vascular analysis in central serous chorioretinopathy. Eur J Ophthalmol 2021;31:2520-27.
27. Kim YH, Lee B, Kang E, et al. Peripapillary choroidal vascularity outside the macula in patients with central serous chorioretinopathy. Transl Vis Sci Technol 2021;10:9.