

Correlation Between Choroidal Structure and Smoking in Eyes With Central Serous Chorioretinopathy

Tatsuya Inoue (✉ inouet-ky@umin.ac.jp)

Yokohama City University Medical Center

Kazuyoshi Okawa

Yokohama City University Medical Center

Ryo Asaoka

University of Tokyo

Keiko Azuma

University of Tokyo

Ryo Obata

University of Tokyo

Rei Arasaki

Yokohama City University Medical Center

Shouko Ikeda

Yokohama City University Medical Center

Arisa Ito

Yokohama City University Medical Center

Maiko Maruyama-Inoue

Yokohama City University Medical Center

Yasuo Yanagi

Yokohama City University Medical Center

Kazuaki Kadonosono

Yokohama City University Medical Center

Research Article

Keywords: choroidal vascularity index, choroidal thickness, central serous chorioretinopathy, smoking

Posted Date: December 11th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-121708/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

A smoking habit is associated with central serous chorioretinopathy (CSC). Although CSC is caused by an abnormal circulation of the choroid, how smoking habit affects the choroid remains elusive. Therefore, to investigate the effect of smoking on the choroidal structure in patients with CSC, the current study analyzed two important choroidal morphological parameters in 75 consecutive CSC patients with/without a smoking habit; i.e., subfoveal choroidal thickness [SFCT] and the choroidal vascular index (CVI), the ratio of the luminal area to the total choroidal area. The results demonstrated that although other baseline parameters (age or refractive error expressed by the spherical equivalent [SE]) was not different between the smoking group and the non-smoking group, the SFCT was thicker in smoking group compared with non-smoking group ($382.0 \pm 68.2 \mu\text{m}$ vs. $339.3 \pm 52.3 \mu\text{m}$, $p = 0.0038$). No significant difference was observed in the CVI ($p = 0.32$). The optimal model for SFCT included the variables of age, SE and a history of smoking among the baseline parameters. Additionally, increased pack years was associated with increased SFCT. Taken together, cigarette smoking is associated with an increased SFCT in patients with CSC. Thicker choroid in smoking CSC patients may be an important modulator of the disease.

Introduction

Central serous chorioretinopathy (CSC) is characterized by serous retinal detachment accompanied by the dysfunction of the retinal pigment epithelium (RPE). Recent studies have clarified the change in the choroid. First, CSC is generally characterized by choroidal vascular hyperpermeability (CVH) on indocyanine green angiography.¹⁻³ Additionally, enhanced depth imaging (EDI-OCT),⁴ which allows for the visualization of the choroidal structure, clarified the ratio of the luminal area to the total choroidal area, known as the choroidal vascular index (CVI) to be increased in CSC. As such, functional and anatomical abnormalities of the choroid (so-called "pachychoroid") are considered to be associated with CSC.^{5,6} Specifically, increased osmotic pressure, presumably due to an increased area of the choroidal vessels, is thought to be associated with choroidal hyperpermeability, causing RPE detachment, leading to the accumulation of fluid in the subretinal space. Interestingly, eyes with acute CSC had a higher CVI than eyes without CSC or eyes with resolved CSC⁷, suggesting that CVI is dynamically associated with CSC, which may change during the course of disease depending on the activity.

A smoking habit is a modifiable risk factor that is associated with CSC.⁸⁻¹¹ Interestingly, recent detailed examinations of choroidal structural changes in healthy smokers has suggested that the CVI was significantly smaller in smokers than in non-smokers whereas the foveal retinal thickness (FRT) and the subfoveal choroidal thickness (SFCT) were unchanged.¹² Although the pathological significance of such differences in healthy subjects remains unclear, it raises a possibility that there may be some differences in the choroidal pathologies of CSC patients between smokers and non-smokers. Interestingly, smoking was reportedly associated with poor visual outcome in CSC patients.¹³ Since the choroidal flow, as well as choroidal thickness, seems to have abnormal regulation in CSC patients, a smoking habit in CSC

patients may be related with not only CVI, but also choroidal thickness. The hypothesis prompted us to investigate the effect of a smoking habit on the choroidal structure, including the choroidal thickness and CVI, in patients with CSC.

Results

Table 1 shows the baseline characteristics of the patients in the present study. Among 75 eyes in 75 CSC patients (58 males and 17 females) with serous retinal detachment (SRD), 45 patients were smokers and 30 patients were non-smokers. Thirty-one patients were current smokers, and the remaining 44 patients were non-current smokers. The mean patient age was 47.1 ± 6.0 years (mean \pm standard deviation). No significant difference in age was seen between the smoking group (47.2 ± 6.3 years) and the non-smoking group (46.8 ± 5.5 years, $p = 0.74$, Wilcoxon rank sum test). The Brinkman index (BI, number of cigarettes smoked per day multiplied by the number of years of smoking) was 221.9 ± 238.6 in the smokers group. The mean spherical equivalent of the refractive error also showed no significant difference between the smoking and non-smoking groups (-1.31 ± 1.80 diopter vs. -2.06 ± 1.84 diopter, $p = 0.10$). A significant difference in the SFCT was seen between the smoker and non-smoker groups ($382.0 \pm 68.2 \mu\text{m}$ vs. $339.3 \pm 52.3 \mu\text{m}$, $p = 0.0038$, Wilcoxon rank sum test, Fig. 1A), while no significant difference was observed in the CVI ($64.6 \pm 2.1\%$ vs. $65.3 \pm 2.3\%$, $p = 0.32$, Fig. 1B).

Table 1
Baseline characteristics of patients

Parameter	Smoking group	Non-smoking group	P value
Number of patients, eyes	45, 45	30, 30	-
Age (years)	47.2 ± 6.3	46.8 ± 5.5	0.74
BI	221.9 ± 238.6	-	-
SE (diopter)	-1.31 ± 1.80	-2.06 ± 1.84	0.10
LogMAR VA	0.057 ± 0.24	-0.000089 ± 0.21	0.11
SFCT (μm)	382.0 ± 68.2	339.3 ± 52.3	0.0038
CVI (%)	64.6 ± 2.1	65.3 ± 2.3	0.32
FRT (μm)	367.8 ± 106.5	360.3 ± 130.1	0.69
BI: Brinkman index, SE: spherical equivalent, logMAR VA: logarithm of the minimum angle of resolution of visual acuity, SFCT: subfoveal choroidal thickness, FRT: foveal retinal thickness, CVI: choroidal vascular index.			

We then investigated factors associated with SFCT. As a result of the bias-corrected Akaike's information criterion (AICc) model selection, the optimal model for SFCT included the variables of age, refractive error expressed by the spherical equivalent (SE), and history of smoking among the variables of age, SE, and history of smoking or hypertension (Table 2). The optimal model formula was as follows:

Table 2
Relationship between smoking and SFCT

Variables	Univariate analysis			The optimal model		
	Coefficient	Stderr	P value	Coefficient	Stderr	P value
Age	-3.39	1.22	0.0070	-3.40	1.12	0.0034
SE	10.64	3.97	0.0091	8.27	3.71	0.029
History of smoking	42.7	14.7	0.0049	37.7	13.9	0.0082
History of hypertension	8.43	22.36	0.71	N.S.	N.S.	N.S.

SFCT: subfoveal choroidal thickness, Stderr: standard error, SE: spherical equivalent, N.S.: not selected.

SFCT = 515.7 - 3.40 x Age (standard error [Stderr] = 1.12, $p = 0.0034$) + 8.27 x SE (Stderr = 3.71, $p = 0.029$) + 37.7 x Smoking (Stderr = 13.9, $p = 0.0082$) (AICc = 827.6).

In the aforementioned analysis, a history of smoking, but not BI, was included in the variable due to colinearity between these two factors. When this analysis was performed using the BI instead of a history of smoking (Table 3), BI was selected as a predictive variable, and the formula for the optimal model for SFCT was as follows:

Table 3
Relationship between BI and SFCT

Variables	Univariate analysis			The optimal model		
	Coefficient	Stderr	P value	Coefficient	Stderr	P value
Age	-3.39	1.22	0.0070	-4.47	1.19	0.00034
SE	10.64	3.97	0.0091	7.79	3.72	0.040
BI	0.063	0.031	0.046	0.088	0.030	0.0052
History of hypertension	8.43	22.36	0.71	N.S.	N.S.	N.S.

BI: Brinkman index, SFCT: subfoveal choroidal thickness, Stderr: standard error, SE: spherical equivalent, N.S.: not selected.

SFCT = 568.5 - 4.47 x Age (Stderr = 1.19, $p = 0.00034$) + 7.79 x SE (Stderr = 3.72, $p = 0.040$) + 0.088 x BI (Stderr = 0.030, $p = 0.0052$) (AICc = 826.7).

On the other hand, the optimal model for CVI included SE and history of smoking among the baseline parameters. The formula for the optimal model was as follows:

CVI = 65.9 + 0.29 x SE (Stderr = 0.14, $p = 0.039$) - 0.90 x Smoking (Stderr = 0.51, $p = 0.083$) (AICc = 331.7)

However, unlike the results for SFCT, when the BI was used instead of a history of smoking, BI was not selected as an explanatory variable for CVI.

Moreover, we investigated the relationship between current smoking and the choroidal structure. No significant differences in SFCT and CVI were seen between current smokers and non-current smokers ($p = 0.56$ [Figure 2] and 0.98 , respectively, Wilcoxon rank sum test). Furthermore, current smoking was not selected for the SFCT and the CVI using AICc model selection (data not shown).

Discussion

In the present study, the relationship between the choroidal structure and cigarette smoking was investigated in patients with CSC. As a result, a history of smoking was significantly correlated with an increased SFCT in CSC eyes with subretinal fluid (SRF). Importantly, the effect of smoking on the SFCT was dose (pack years) - dependent as shown in the prediction model, suggesting the association was not a mere chance finding. On the other hand, the presence of a history of smoking was associated with a decreased CVI.

The subfoveal choroid is significantly thicker in eyes with CSC,^{14,15} and the resolution of CSC is reportedly correlated with a reduction in the SFCT.^{16,17} Moreover, a previous report suggested that the CVI was higher in acute CSC eyes, compared with contralateral non-CSC eyes.⁷ Our present results demonstrated that the presence of a history of smoking was correlated with an increased SFCT and a decreased CVI, suggesting that the pathology of CSC may be somewhat different between smokers and non-smokers. Although there is no direct link between visual acuity and the choroidal thickness, corroborating evidence from prior observations¹⁴⁻¹⁷ suggest that choroidal thickness may be associated with disease activity; our findings may in part explain why the smoking was reportedly associated with poor visual outcome in CSC patients.¹³

Previous studies have investigated the effect of smoking on the CVI, with varying results in normal subjects. Agrawal et al. reported that a univariate analysis demonstrated a significant correlation between cigarette smoking and the CVI, while a multivariate analysis showed no significant correlation.¹⁸ On the contrary, Wei et al. suggested that smoking was associated with a smaller CVI in normal eyes.¹² Regarding CVI in CSC patients, a previous study reported that the CVI was increased in patients with acute CSC, compared with contralateral non-CSC eyes, suggesting the possibility that the CVI was influenced by the activity of CSC and vice versa.⁷ In contrast, our present results for eyes with CSC suggested that the CVI was negatively associated with a smoking history. This apparent contradiction may be reconciled by the fact that the choroid in CSC patients are hyperpermeable. We assume it rational to consider that luminal area increase in the smoking group was accompanied by an increase in the stromal area as well because of the increased choroidal vascular permeability in CSC patients, especially among smokers. This is supported by several findings. First, the decreased CVI reflects an increase in the choroidal stromal area. Second, cigarette smoking increases vascular permeability in other organs by

impairing endothelial cell barrier function.¹⁹ Indeed, another report suggested that cigarette smoke extract increases the hyperpermeability of cerebral endothelial cells.²⁰ The present study corroborates these findings, although further studies need to measure the choroidal vascular hyperpermeability to confirm the hypothesis. Furthermore, it would be an interesting topic for the future study to investigate whether a smoking habit is causal to the decreased CVI over the course of a long-term follow-up period. In this regard, however, it should be noted that no significant association was observed between the BI and the CVI in the current study.

The present study had some limitations. First, this study was retrospective in nature, and the number of subjects was relatively small. Second, the choroidal structure in eyes with CSC is associated with the disease duration,²¹ however, this information was not available in the current study. Smoking cessation is usually recommended to CSC patients in clinical settings, however its effectiveness remains elusive. It would be interesting to examine the choroidal structural changes in eyes with CSC that are caused by smoking cessation.

In conclusion, cigarette smoking was associated with an increased subfoveal choroidal thickness in CSC patients. Smoking might be an important factor to modulate CSC by influencing the choroidal thickness.

Methods

The present study was a cross-sectional study conducted at a single center. The medical records of patients with CSC were retrospectively reviewed. This study was approved by the Ethics Committee of the Yokohama City University Medical Center. The study protocol adhered to the tenets of the Declaration of Helsinki and informed consent was obtained from all eligible patients.

All the patients underwent a comprehensive ophthalmic examination including visual acuity, refractive error measurement, and OCT measurement, and the diagnosis of CSC was made based on OCT, fluorescein angiography, and indocyanine green angiography findings. Spectral domain OCT (Spectralis, Heidelberg Engineering) was used to measure the FRT, and the SFCT was estimated using an EDI technique. EDI-OCT examinations were performed between 9:00 and 11:00 a.m. because choroidal thickness is known to exhibit diurnal fluctuations.²² The exclusion criteria were as follows: (1) the absence of a detailed medical history; (2) a history of previous ocular surgery (other than uncomplicated cataract surgery) or other retinal disorders; (3) the presence of high myopia (-6.0 diopter or greater), and (4) the presence of choroidal neovascularization and polypoidal choroidal vasculopathy.

Binarization of the OCT images was performed to calculate the total choroidal area, stromal area, luminal area and CVI, as previously reported.²³ Briefly, the choroidal area of the horizontal EDI-OCT images across the fovea was binarized using the Niblack method with ImageJ software (Fig. 3). The images were converted to 8 bits, and the Niblack auto-local threshold was applied to binarize the images to separate the choroidal luminal and stromal areas. Then, CVI was calculated as luminal pixels/total choroidal pixels.

Statistical analyses

Baseline parameters (age, refractive error, logMAR visual acuity, FRT, SFCT and CVI) were compared between smokers and non-smokers using the exact Wilcoxon rank sum test. In addition, the associations between SFCT and CVI and the baseline parameters (age, refractive error, and history of smoking) were analyzed using a multivariate linear regression. Subsequently, model selection was performed to identify the optimal linear regression model using the AICc index from all 2^4 patterns consisting of four variables (age, refractive error, history of smoking/hypertension). The AIC is a well-known statistical measurement used in model selection, and the AICc is a corrected version of the AIC that provides an accurate estimation even when the sample size is small.^{24, 25} The variables selected using this model were regarded as being statistically significant. All statistical analyses were performed using the statistical programming language R (ver. 3.4.3, The R Foundation for Statistical Computing, Vienna, Austria).

Declarations

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

K.O.(first author) conducted the experiment, wrote the manuscript and prepared the figures and tables; T.I. (corresponding author), R.A., M.I., K.K. and Y.Y. conceived the experiment, analyzed the results and wrote the manuscript. K.A., R.O., R.A., S.I. and A.I. conducted the experiment and analyzed the results. All authors reviewed the manuscript.

Summary statement:

This study aimed to investigate the effect of smoking on the choroidal structure, including the subfoveal choroidal thickness and the choroidal vascular index in CSC. Our result suggested smoking was associated with an increased subfoveal choroidal thickness in patients with CSC. Smoking habit influences the choroidal thickness in CSC.

References

1. Guyer DR, Yannuzzi LA, Slakter JS, Sorenson JA, Ho A, Orlock D. Digital indocyanine green videoangiography of central serous chorioretinopathy. *Arch Ophthalmol.* **112**, 1057-1062 (1994).
2. Piccolino FC, Borgia L. Central serous chorioretinopathy and indocyanine green angiography. *Retina.* **14**, 231-242 (1994).
3. Iida T, Kishi S, Hagimura N, Shimizu K. Persistent and bilateral choroidal vascular abnormalities in central serous chorioretinopathy. *Retina.* **19**, 508-512 (1999).

4. Spaide RF, Koizumi H, Pozzoni MC, Pozzoni MC. Enhanced depth imaging spectral-domain optical coherence tomography. *Am J Ophthalmol.* **146**, 496-500 (2008).
5. Liegl R, Ulbig MW. Central serous chorioretinopathy. *Ophthalmologica.* **232**, 65-76 (2014).
6. Ferrara D, Waheed NK, Duker JS. Investigating the choriocapillaris and choroidal vasculature with new optical coherence tomography technologies. *Prog Retin Eye Res.* **52**, 130-155 (2016).
7. Agrawal R, Chhablani J, Tan K-A, Shah S, Sarvaiya C, Banker A. CHOROIDAL VASCULARITY INDEX IN CENTRAL SEROUS CHORIORETINOPATHY. *Retina.* **36**, 1646-1651 (2016).
8. Burns DM. Cigarettes and cigarette smoking. *Clin Chest Med.* **12**, 631-642 (1991).
9. 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.* **103**, 725-729 (2019).
10. Chakravarthy U, Wong TY, Fletcher A, et al. Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis. *BMC Ophthalmol.* **10**, 31 (2010).
11. Seddon JM, George S, Rosner B. Cigarette smoking, fish consumption, omega-3 fatty acid intake, and associations with age-related macular degeneration: the US Twin Study of Age-Related Macular Degeneration. *Arch Ophthalmol.* **124**, 995-1001 (2006).
12. Wei X, Kumar S, Ding J, Khandelwal N, Agarwal M, Agrawal R. Choroidal Structural Changes in Smokers Measured Using Choroidal Vascularity Index. *Invest Ophthalmol Vis Sci.* **60**, 1316-1320 (2019).
13. [Effects of smoking on visual acuity of central serous chorioretinopathy patients.](#) Türkcü FM, Yüksel H, Sahin A, Cinar Y, Cingü K, Arı S, Sahin M, Altındağ S, Caça I. *Cutan Ocul Toxicol.* **33**, 115-119 (2014).
14. Kim YT, Kang SW, Bai KH. Choroidal thickness in both eyes of patients with unilaterally active central serous chorioretinopathy. *Eye (Lond).* **25**, 1635-1640 (2011).
15. Maruko I, Iida T, Sugano Y, Ojima A, Sekiryu T. Subfoveal choroidal thickness in fellow eyes of patients with central serous chorioretinopathy. *Retina.* **31**, 1603-1608 (2011).
16. Kim YK, Ryoo NK, Woo SJ, Park KH. Choroidal Thickness Changes After Photodynamic Therapy and Recurrence of Chronic Central Serous Chorioretinopathy. *Am J Ophthalmol.* **160**, 72-84 (2015).
17. Kang NH, Kim YT. Change in subfoveal choroidal thickness in central serous chorioretinopathy following spontaneous resolution and low-fluence photodynamic therapy. *Eye (Lond).* **27**, 387-391 (2013).
18. 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.* **6**, 21090 (2016).
19. Lu Q, Gottlieb E, Rounds S. Effects of cigarette smoke on pulmonary endothelial cells. *Am J Physiol Lung Cell Mol Physiol.* **314**, 743-756 (2018).

20. Bernard A, Ku JM, Vlahos R, Miller AA. Cigarette smoke extract exacerbates hyperpermeability of cerebral endothelial cells after oxygen glucose deprivation and reoxygenation. *Sci Rep.* **9**, 15573 (2019).
21. Hanumunthadu D, van Dijk EHC, Dumpala S, et al. Evaluation of Choroidal Layer Thickness in Central Serous Chorioretinopathy. *J Ophthalmic Vis Res.* **14**, 164-170 (2019).
22. Tan CS, Ouyang Y, Ruiz H, Sadda SR. Diurnal variation of choroidal thickness in normal, healthy subjects measured by spectral domain optical coherence tomography. *Invest Ophthalmol Vis Sci.* **53**, 261-266 (2012).
23. Azuma K, Tan X, Asano S, et al. The association of choroidal structure and its response to anti-VEGF treatment with the short-time outcome in pachychoroid neovascularopathy. *PLoS One.* **14**, e0212055 (2019).
24. Nakagawa S, Schielzeth H. A general and simple method for obtaining R2 from generalized linear mixed-effects models. *Methods in Ecology and Evolution.* **4**, 133-142 (2013).
25. Burnham KP, Anderson DR. Multimodel Inference: Understanding AIC and BIC in Model Selection. *Sociological Methods & Research.* **33**, 261-304 (2004).

Figures

Figure 1

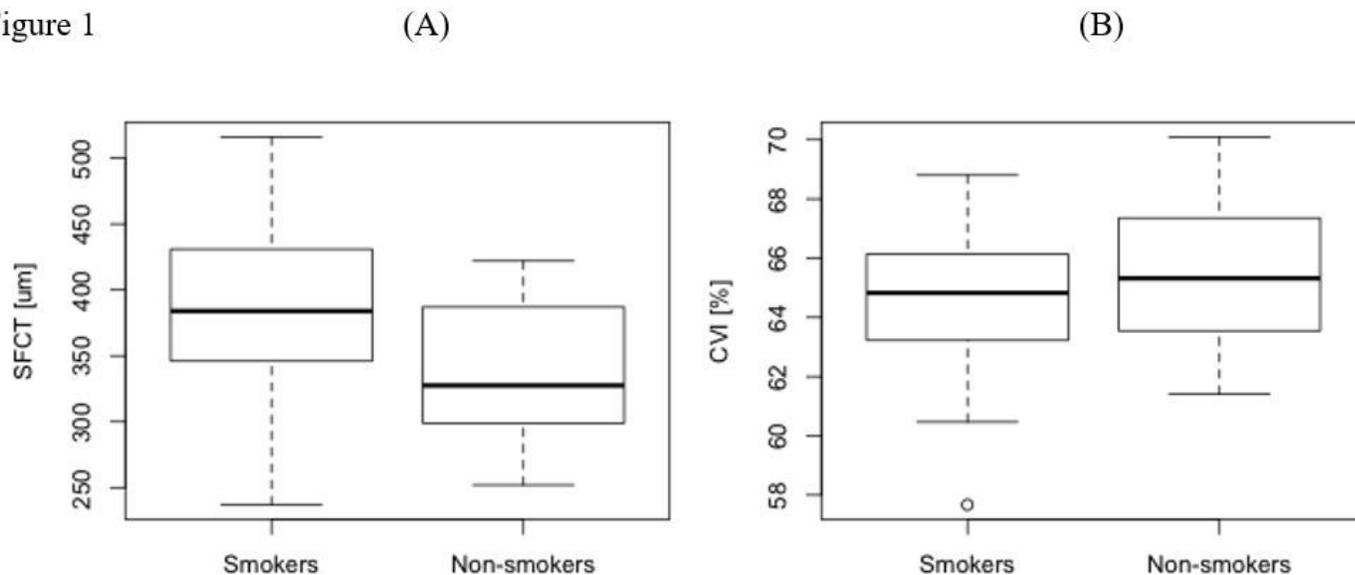


Figure 1

Comparison of SFCT and CVI between smokers and non-smokers in patients with CSC. A significant difference in SFCT was seen between smokers and non-smokers (A, $p = 0.0038$, Wilcoxon rank sum test),

but no significant difference in CVI was seen (B, $p = 0.32$, Wilcoxon rank sum test). SFCT, subfoveal choroidal thickness; CVI, choroidal vascular index; CSC, central serous chorioretinopathy

Figure 1

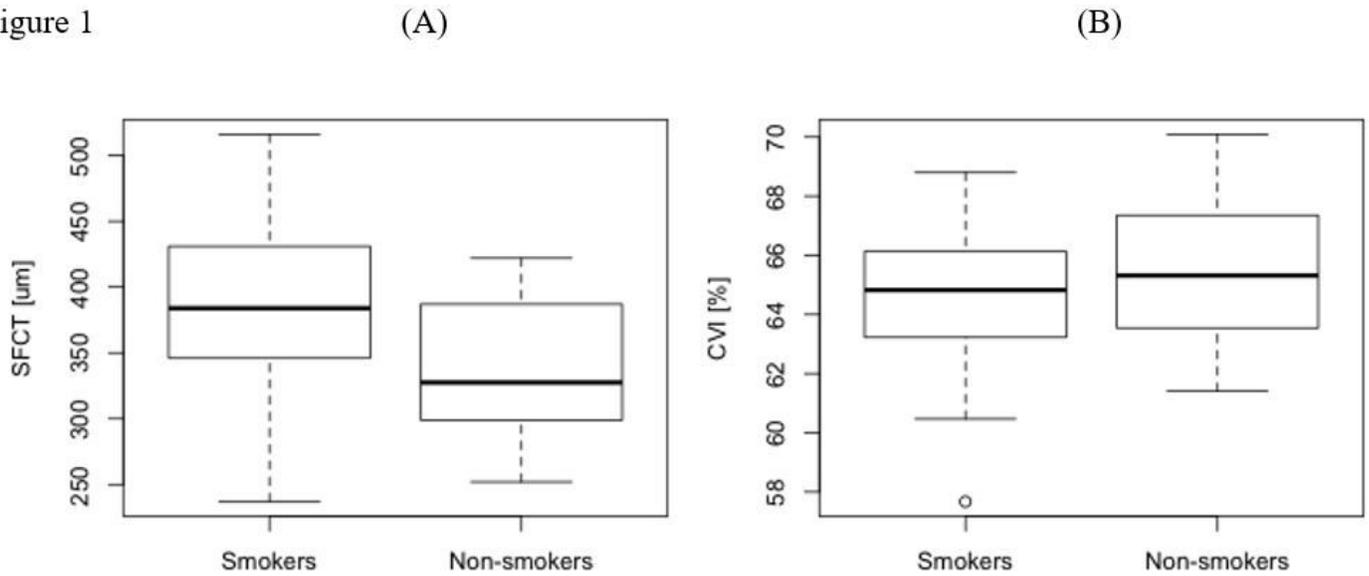


Figure 1

Comparison of SFCT and CVI between smokers and non-smokers in patients with CSC. A significant difference in SFCT was seen between smokers and non-smokers (A, $p = 0.0038$, Wilcoxon rank sum test), but no significant difference in CVI was seen (B, $p = 0.32$, Wilcoxon rank sum test). SFCT, subfoveal choroidal thickness; CVI, choroidal vascular index; CSC, central serous chorioretinopathy

Figure 2

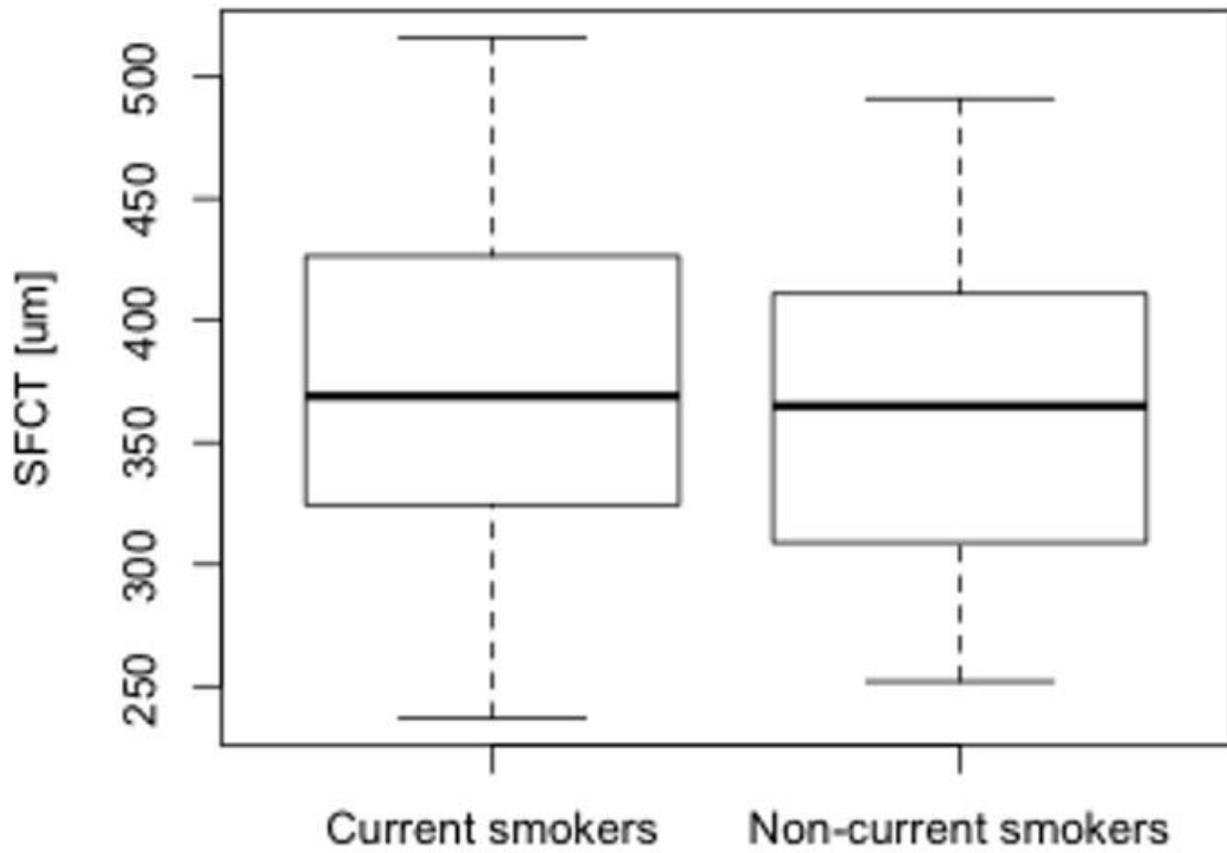


Figure 2

Comparison of SFCT between current and non-current smokers in patients with CSC. No significant difference in SFCT was seen between current and non-current smokers ($p = 0.56$, Wilcoxon rank sum test). SFCT, subfoveal choroidal thickness; CSC, central serous chorioretinopathy

Figure 2

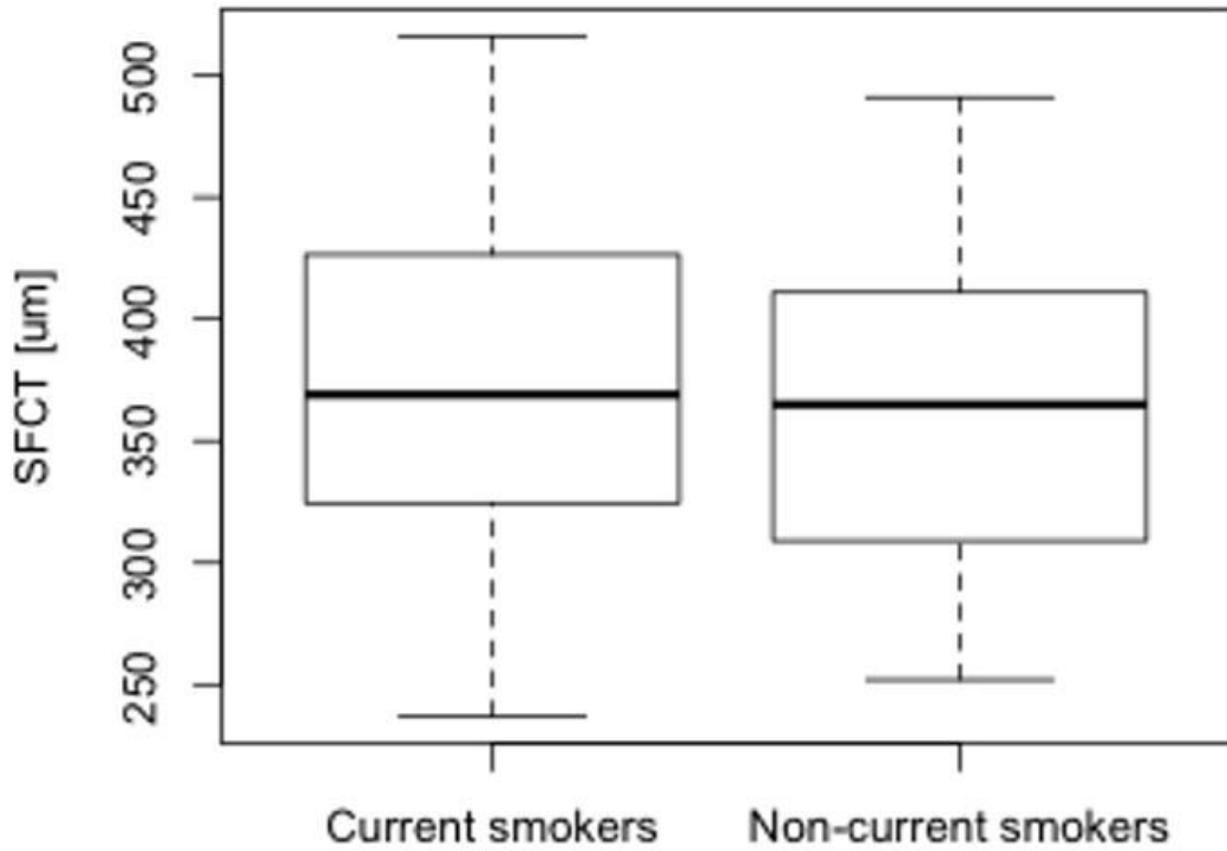


Figure 2

Comparison of SFCT between current and non-current smokers in patients with CSC. No significant difference in SFCT was seen between current and non-current smokers ($p = 0.56$, Wilcoxon rank sum test). SFCT, subfoveal choroidal thickness; CSC, central serous chorioretinopathy

Figure 3

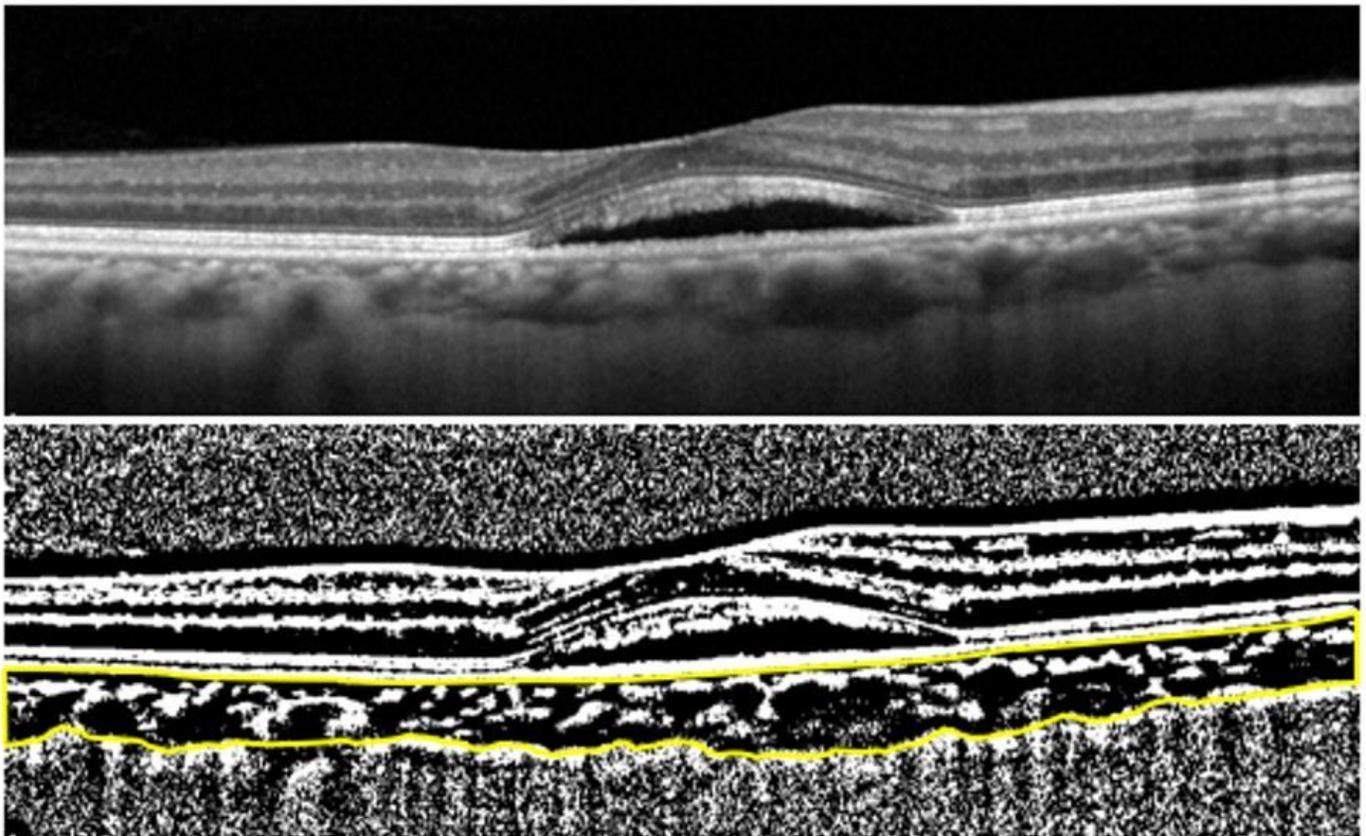


Figure 3

Binarization of an OCT image in a patient with CSC. (A) Representative image of the horizontal EDI-OCT scan in CSC eye with serous retinal detachment. (B) Binarized OCT image using Niblack method. Yellow line indicates the border of the choroid. Subsequently, the CVI was calculated as luminal (black) pixels/total choroidal pixels in each eye. CSC, central serous chorioretinopathy; CVI, choroidal vascular index

Figure 3

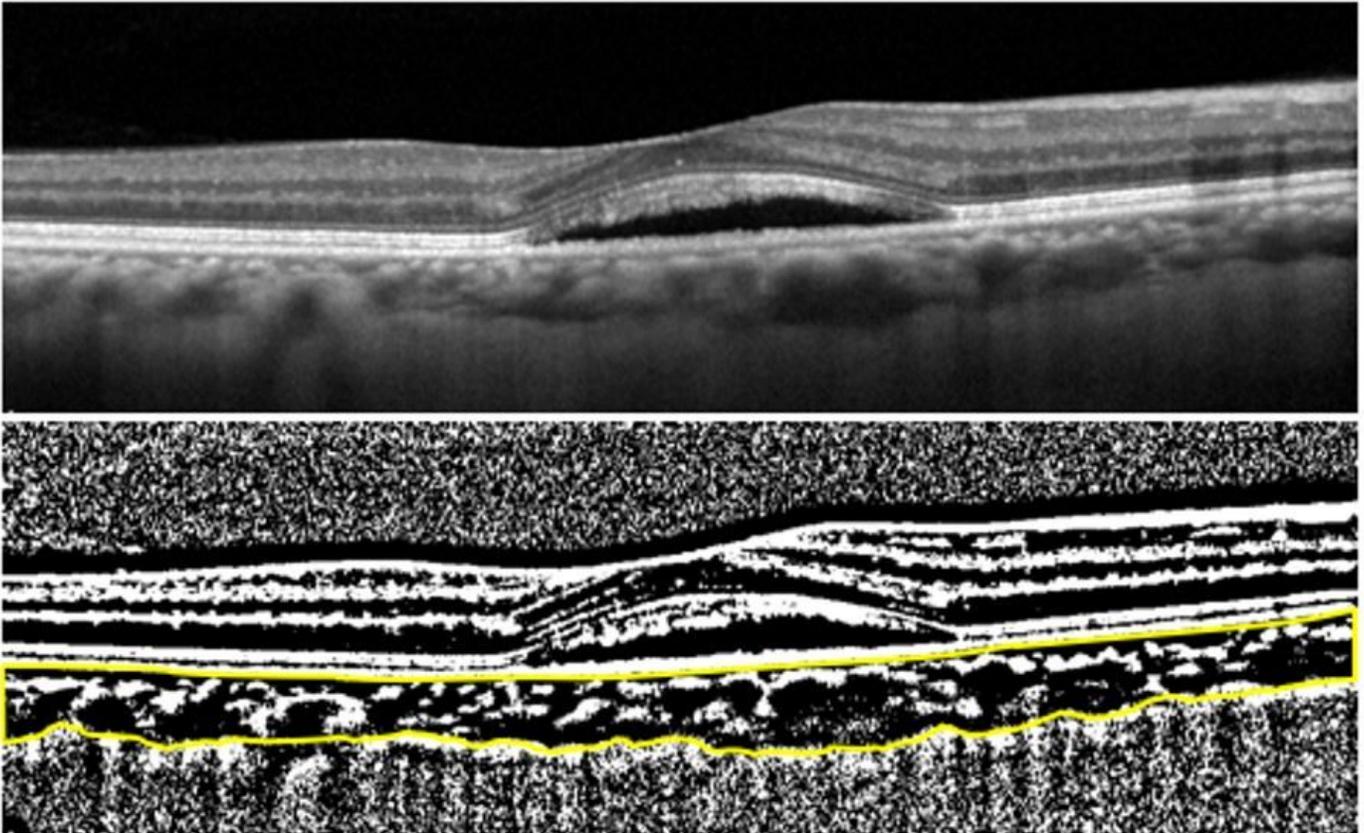


Figure 3

Binarization of an OCT image in a patient with CSC. (A) Representative image of the horizontal EDI-OCT scan in CSC eye with serous retinal detachment. (B) Binarized OCT image using Niblack method. Yellow line indicates the border of the choroid. Subsequently, the CVI was calculated as luminal (black) pixels/total choroidal pixels in each eye. CSC, central serous chorioretinopathy; CVI, choroidal vascular index