Choroidal Features of Healthy Iranian Individuals

Ali Banafsheafshan[1], Haniyeh Zeidabadinejad[2], Masoud Mirghorbani[1], Hooshang Faghihi[1], Elias Khalili Pour[1], Hamid Riazi-Esfahani[1]

[1]Retina and Vitreous Service, Department of Ophthalmology, Farabi Eye Hospital, Tehran, Iran, [2]Eye Research Center, Farabi Eye Hospital, Tehran, Iran

Abstract

Purpose: To assess subfoveal choroidal thickness (SFCT) and choroidal vascularity index (CVI) profile in the Iranian healthy population and assessment of the inter-eye difference in this regard.

Methods: In a cross-sectional study, 141 healthy subjects underwent an assessment of refraction and best-corrected visual acuity (BCVA), axial length (AL), and measurement of the intraocular pressure. The imaging of the choroid was performed using the enhanced-depth imaging mode of Spectralis optical coherence tomography from the foveal slab to measure SFCT and calculate CVI.

Results: A total of 282 eyes of 141 healthy subjects (59.6% men, mean age of 60.86 ± 11.46 years) enrolled in the current study. The mean SFCT of the right and left eye was 247.40 ± 70.37 and 251.25 ± 72.19, respectively. The mean CVI of the right and left eye was 62.63 ± 3.77 and 63.19 ± 3.91, respectively. None of the measured parameters had statistically significant differences between the left and right eyes. In both univariate and multivariate regression analysis, CVI was significantly associated with BCVA ($P < 0.001$) but was not associated with age, spherical equivalent (SE), gender, central macular thickness (CMT), and SFCT. In univariate regression analysis, SFCT was significantly associated with age, refraction ($P = 0.02$), BCVA ($P = 0.003$), AL ($P < 0.001$), and CVI ($P = 0.02$) but not significantly associated with gender and CMT. In multivariate analysis, age ($P < 0.001$), gender ($P = 0.001$), and AL ($P < 0.001$) were significantly associated with SFCT, but SE, BCVA, CVI, and CMT were not significantly associated.

Conclusions: This was the first investigation to assess the SFCT and CVI simultaneously in the Iranian population to establish a normative database for future studies. CVI was less variable than SFCT in a healthy population, and no statistically significant differences existed between the left and right eyes.

Keywords: Choroidal vascularity index, Enhanced-depth imaging mode of Spectralis optical coherence tomography, Iranian, Subfoveal choroidal thickness

Address for correspondence: Elias Khalili Pour, Retina and Vitreous Service, Farabi Eye Hospital, Qazvin Square, Tehran, Iran.
E-mail: ekhalilipour@gmail.com
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Introduction

Choroid is a vital tissue that serves a crucial part in maintaining appropriate visual function. It supplies essential nutrients and oxygen to the retina, with the highest blood flow of any tissue in the human body.[1] Many eye diseases, such as age-related macular degeneration (AMD), central serous chorioretinopathy (CSCR), and polypoidal choroidal vasculopathy (PCV), can result from structural or functional changes in the choroid.[2-4]

Subfoveal choroidal thickness (SFCT) and choroidal vascularity index (CVI) are two essential metrics used to analyze the choroid in optical coherence tomography (OCT) Images.[5,6] Both of these metrics are useful for studying the choroid, but they have different clinical implications and levels of relevance.[7] SFCT is measured by OCT as the distance between the posterior edge of the retinal pigment epithelium (RPE) and the choroid–sclera interface.[2] Many ocular conditions, including AMD, myopia, and CSCR, have been associated with choroidal thickness variations.[2,4,8] Instead, the CVI is a relatively recent and more sensitive metric that offers information on the choroidal vascular anatomy.[6] It is

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assessed using binarization techniques of OCT images and is defined as the proportion of the luminal area (LA) to the total choroidal area (TCA).[7,9,10]

Investigations of ocular diseases that affect only one eye or that begin unilaterally but progress bilaterally necessitate the identification of asymmetrical or unilateral characteristics between fellow eyes. It is essential to establish a baseline of interocular asymmetry in normal eyes that can be used to assist clinicians and researchers in distinguishing between pathological and physiological asymmetries. Using OCT, previous research has demonstrated that some degrees of nonpathologic asymmetry can exist in the retina and choroid between fellow eyes.[11,12]

This study aimed to assess the SFCT and CVI in the Iranian healthy population and assessment of inter-eye differences in this regard. The objective of our study was to establish a normative database for CVI and identify factors associated with CVI in individuals with healthy eyes.

Methods

This study is a cross-sectional investigation of healthy adults in Farabi Eye Hospital in Tehran, Iran. The research was carried out in accordance with the principles outlined in the Declaration of Helsinki and was approved by an ethics committee (ethics approval code: IR.TUMS.FARABIH.REC.1401.023). The subjects provided written informed consent subsequent to a comprehensive explanation of the study's particulars, potential risks, and consequences.

The study participants comprised individuals who were at least 18 years old and accompanied patients to Farabi Eye Hospital ophthalmology clinics. According to their own reports, all participants were in good health. Every subject had presented for their routine ocular examination between May 1, 2020, and December 31, 2021. All participants underwent a complete ophthalmic examination. Refraction and best-corrected visual acuity (BCVA) were measured using the Snellen chart, and the results were then converted to a logMAR. Spherical equivalent (SE) was calculated as the sum of the spherical power and half of the cylinder power. Patients were classified according to SE into four groups: hyperopia > +1 diopter (D), +1 D ≥ SE ≥ −1 D, −1 D > SE ≥ −6 D, and myopia > −6 D. The measurement of ocular biometry, which encompasses axial length (AL), was conducted through noncontact partial coherence interferometry utilizing the IOL Master V3.01, (Carl Zeiss Meditec AG in Jena, Germany). The Goldmann applanation tonometry (Haag-Streit, Bern, Switzerland) was employed to measure the intraocular pressure (IOP) before pupil dilation.

Exclusion criteria included a history of systemic diseases such as diabetes mellitus, hypertension, obesity (body mass index >30), history of glaucoma, evidence of vitreoretinal diseases such as AMD, and diabetic retinopathy, epiretinal membrane, previous ocular surgery, patients with any part of pachychoroid spectrum, and Spectralis OCT imaging with a quality index <18 decibels.

The imaging of the choroid was performed using the enhanced depth imaging mode of spectral-domain-OCT (SD-OCT) (Spectralis, Heidelberg Engineering, Heidelberg, Germany) enhanced-depth imaging mode of Spectralis OCT (EDI-OCT). Macular scanning was done using seven horizontal line scans (30° × 5°) centered on the fovea, with 100 frames averaged in each B-scan. Each scan was 8.9 mm long and spaced 240 µm apart.

SFCT defined as the distance between the outer border of Bruch's membrane-RPE complex and the innermost border of the choroidoscleral junction in the subfoveal region, was measured manually using built-in calipers in OCT software. All manual segmentations, including the delineation of RPE and sclerochoroidal boundaries, were performed by a competent grader (AB) and double-checked by a second independent grader (EKP). In the event of a disagreement, the contours were segmented by consensus. Because choroidal structures exhibit diurnal variations,[13,14] all EDI-OCT scans were conducted between 9:00 AM and 12:00 AM.

Distinguishable subfoveal choroidal images on EDI-OCT were chosen for review to calculate CVI using Sonoda's Method.[9] These images were identified independently by unmask evaluators. In EDI-OCT images, the upper edge of the region of interest (ROI) corresponded to the RPE, while the lower edge corresponded to the choroidoscleral border. The nasal margin was the optic nerve head, while the temporal margin was 8 mm temporal of the optic nerve head. The OCT instrument's built-in auto-adjust function determined the distance. As reported, the choroidal region of the OCT image was binarized using a modified Niblack procedure.[7] The OCT image was briefly analyzed using (FIJI [an expanded version of ImageJ software], version 1.51 h; National Institutes of Health, Bethesda, Maryland) available at http://imagej.nih.gov/Fiji/. The ROI manager selected and set an ROI in the OCT image. Then, three choroidal vessels with lumens larger than 100 m were chosen randomly using the oval selection tool on the interface, and the software determined the average reflectivity of these regions. To minimize disturbance in the OCT image, the minimum value for the average luminance was set to 0. The image was then converted to 8 bits and adjusted using Niblack's auto-local threshold. The binarized image was reconverted to an RGB image, and the luminance region was identified using the color thresholding tool. The white pixels were classified as choroidal stroma or interstitial area, while the dark pixels were classified as LAs. Automatically computed were the TCA, the LA, and the stromal area. The ratio of LA to TCA is called the CVI.

To evaluate inter-rater reliability for SFCT measurement and CVI measurement, the absolute agreement model of the interclass correlation coefficient was applied to 20 segmented EDI-OCT images by two independent evaluators. A correlation value between 0.81 and 1.00 denotes a strong relationship.

Statistical analysis

Statistical analysis was performed using SPSS version 20.0 (SPSS, Inc., Chicago, IL, USA). Mean and standard deviation were recruited to describe the data. Due to the different measurement units of CVI and SFCT, the coefficient of variation (COV) was used to compare the variability between CVI and SFCT. As both eyes of patients were included, to compensate for the inter-correlation between the right and left eyes of the same patient, generalized estimating equations (GEE) analysis was provided. We used univariate and multivariable GEE regression analyses to determine the associations of SFCT and CVI (dependent variables) with ocular and systemic factors (independent variables). Factors that showed a significant association in univariate analysis ($P < 0.10$) was included for multiple GEE regression. All P values were two-tailed and were considered statistically significant if values were <0.05.

Results

A total of 296 eyes from 148 healthy subjects (yielding a cooperation rate of 53.8%) participated in the survey between May 1, 2020, and December 31, 2021. Out of these 296 eyes, 14 (4.7%) were excluded due to inadequate scan quality. The analysis focused on the remaining 282 eyes, with a distribution of 59.6% men and a mean age of 60.86 ± 11.46 years (range, 32–87 years), all of which had high-quality EDI-OCT scans suitable for assessment.

Inter-rater reliability assessment of CVI and SFCT measurements showed interclass correlations of 0.969 (95% confidence interval [CI]: 0.91–0.98) and 0.988 (95% CI: 0.97–0.99), respectively.

The demographic and EDI-OCT parameters of patients in the study are summarized in Table 1. The mean SE refractive error was −1.24 ± 1.9 D (range, −14.3 to + 7.8 D). The prevalence of myopia (SE < −0.5 D) and high myopia (SE < −6.0 D or AL >26.5 mm) was 29.8% and 5.3%, respectively.

Figure 1 depicts changes in mean AL in section (a), mean CVI in section (b), mean central macular thickness (CMT), and mean SFCT in section (c). These changes are reported based on the subgrouping of individuals into 10-year interval (31–40, 41–50, etc.).

In univariate GEE regression analysis, CVI was significantly associated with BCVA ($P < 0.001$) but not with age, SE, gender, CMT, and SFCT. In multivariate GEE analysis, CVI was also significantly associated with BCVA ($P < 0.001$). In univariate GEE regression analysis, SFCT was significantly associated with age, SE, BCVA, AL, and CVI but not significantly associated with gender and CMT. In multivariate analysis, age, gender, and AL were also significantly associated with SFCT ($P < 0.001$ for all), but SE, BCVA, CVI, and CMT were not significantly associated [Table 2].

Discussion

A normative database provides a comparative standard for medical evaluations, making identifying subtle changes that may indicate the onset of a disease or disorder easier. Without it, clinicians may struggle to identify abnormalities in individual patients, leading to underdiagnosis, misdiagnosis, or delayed diagnosis. For SFCT and CVI, normative databases are essential for determining whether a patient's choroid's measured thickness or vascularity falls within the normal range.

CVI offers information on the choroidal vessel's real area, which indicates its function. In contrast, choroidal thickness assesses simply the morphological thickness of the choroid, which may not always indicate changes in its function. CVI measures are more trustworthy and reproducible than choroidal thickness measurements. The CVI has been quantified in various ocular conditions affecting the retina and choroid, including but not limited to uveitis, AMD, retinal vascular occlusion, diabetic retinopathy, and CSCR.[6,7,15] A study by

Table 1: Demographic and measured parameters of patients; none of the parameters had statistically significant differences between the left and right eyes

	Mean±SD	Range	Eye	Mean±SD	Diff	95% CI		*P**
						Lower	Upper	
Age	60.86±11.46	32–87						
VA (logMAR)	0.33±0.27	0.0–1.0	OD	0.32±0.28	−0.01	−0.08	0.04	0.37
			OS	0.34±0.26				
AL (mm)	23.24±1.12	18.83–27.48	OD	23.24±1.10	0.01	−0.25	0.28	0.96
			OS	23.23±1.14				
CMT (µm)	263.74±31.89	199–378	OD	264.77±25.30	−4.54	−12.84	1.28	0.30
			OS	269.31±29.21				
CVI	62.91±3.84	51–79	OD	62.63±3.77	−0.55	−1.47	0.36	0.19
			OS	63.19±3.91				
SFCT (µm)	249.34±71.19	100–463	OD	247.40±70.37	−3.84	−20.87	13.17	0.81
			OS	251.25±72.19				

*Mann–Whitney test. Diff: Mean difference, VA: Visual acuity, AL: Axial length, CMT: Central macular thickness, CVI: Choroidal vascular index, SFCT: Subfoveal choroidal thickness, SD: Standard deviation, CI: Confidence interval, OD: Right eye, OS: Left eye

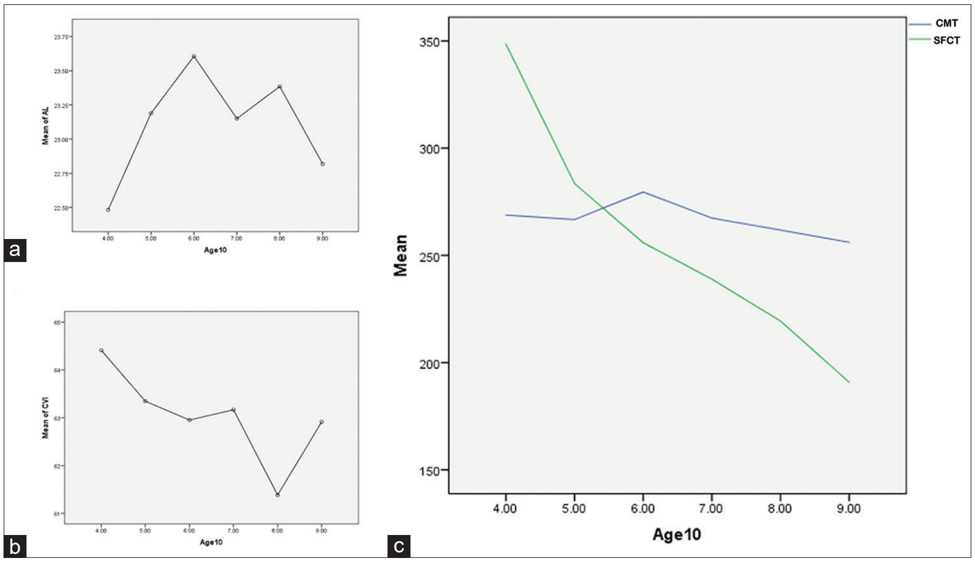

Figure 1: Illustrates the variations in axial length in section (a). The mean choroidal vascularity index (CVI) in section (b) and the central macular thickness (CMT) and subfoveal choroidal thickness (SFCT) in section (c). These changes are presented based on the division of participants into subgroups according to 10-year intervals (31–40, 41–50, etc.). The image illustrates that SFCT and CVI exhibit a declining pattern as age increases, but CMT demonstrates a rather consistent tendency with increasing age

Table 2: Generalized estimating equations univariate and multivariate analysis of choroidal vascular index and subfoveal choroidal thickness associations

	Univariate analysis				Multivariate analysis			
	CVI		SFCT		CVI		SFCT	
	B coefficient	*P*	*B* coefficient	*P*	*B* coefficient	*P*	*B* coefficient	*P*
Age								
>60	0.385	0.54	45.549	0.001	−0.08	0.89	52.34	<0.001
<60	0[a]		0[a]		0[a]		0[a]	
Gender								
Male	−0.1720	0.80	13.958	0.31	−0.35	0.56	37.41	0.001
Female	0[a]		0[a]		0*		0[a]	
SE								
Group 1	−1.791	0.12	−60.950	0.02	0.35	0.81	−3.30	0.87
Group 2	−0.848	0.34	−36.685	0.08	0.06	0.93	−22.81	0.10
Group 3	−1.351	0.11	−11.573	0.56	−1.30	0.08	−1.22	0.93
Group 4	0[a]		0[a]		0[a]		0[a]	
BCVA (logMAR)	−3.391	0.000	−68.236	0.003	−3.61	<0.001	−10.56	0.61
AL	−0.535	0.04	−22.012	0.000	−0.23	0.44	−23.67	<0.001
CMT	−0.007	0.54	0.005	0.97	0.00	0.85	−0.130	0.44
SFCT	0.011	0.02	-	-	0.00	0.10	-	-
CVI	-	-	3.837	0.02	-	-	2.25	0.10

[a]Set to zero because this parameter is redundant. CVI: Choroidal vascular index, SFCT: Subfoveal choroidal thickness, SE: Spherical equivalent, BCVA: Best-corrected visual acuity, AL: Axial length, CMT: Central macular thickness, *All P values were considered statistically significant if values were <0.05.

Agrawal and colleagues revealed that the CVI remained unaltered, while the SFCT was influenced by several factors.[4] Moreover, the authors proposed that the CVI exhibits greater resilience as a diagnostic indicator for pathologies affecting the choroid. The study conducted by Breher and colleagues demonstrated that CVI measurements exhibited minimal variability across subfields, in contrast to choroidal thickness.[16] It has been demonstrated that CVI is a less variable and more reliable and accurate method for detecting and monitoring the progression of ocular disorders such as PCV and AMD.[6,17,18] However, additional investigations are necessary to elucidate the correlation between these two biomarkers acquired from OCT images and their respective functions in healthy populations and the pathophysiology of abnormal ocular conditions.

In healthy eyes, on a single cross-sectional scan, nearly two-thirds (66%) of the subfoveal choroid is vascular, according to previous studies.[9] CVI exhibited less variability and was influenced by fewer physiologic factors than SFCT, indicating that CVI is a relatively stable index for investigating choroidal changes and an independent surrogate marker for assessing choroidal health in future research.

Based on the findings of the present investigation, CVI had a lower COV than SFCT (6.10 vs. 28.55). In contrast to SFCT, which was affected by multiple physiological factors such as age, gender, and AL, CVI was only affected by BCVA. Contrary to the findings of Agrawal *et al*., who found that distinct physiological parameters (AL, IOP, age, and luminal choroidal area) were significantly associated with SFCT; CVI was only significantly associated with SFCT. A higher CVI was substantially associated with a ticker SFCT.[7] Oh *et al*. reported no significant correlations between CVI and age or retinal vascular parameters, except a negative correlation between CVI and the area of the foveal avascular zone as measured by OCTA.[19]

Using SD-OCT, Heirani *et al*. investigated the SFCT and its association with age, gender, SE, and AL in an Iranian population cohort on 469 right eyes with varying refractive statuses. In contrast to our study which enrolled patients with >32 years old, they included patients between the ages of 4 and 60, and found that the mean SFCT was 329.83 ± 70.33 m.[20] In another study conducted by Entezari *et al*., the mean age of enrolled healthy individuals was 34.6 ± 9.8 years (range, 18–57 years), and the mean SFCT was 363 ± 84 μm.[21] In our study, the mean SFCT was 249.34 ± 71.190 m. This difference can be attributed to the age range of patients or the difference in the mean of refractive error of individuals included in the different studies. It is important to note that SFCT measurements may vary depending on the imaging technology used, age, gender, and other demographic and environmental factors.

Choroidal diseases, such as AMD, CSCR, and PCV, can be unilateral, bilateral, or manifest unilaterally at first but then progress bilaterally.[12,22,23] In normal-appearing eyes, the appearance of bilateral differences in choroidal measurements between fellow eyes that exceed the range of physiological asymmetry may be the first indication of an evolving pathological process requiring further evaluation and monitoring.[12] Establishing baseline choroidal asymmetry between fellow eyes in the normal population may be of clinical value, particularly when monitoring for the advent of diseases that typically affect both eyes.[12] Although there was no statistically significant difference between the SFCT and CVI according to the laterality of the eyes in the current study, interocular differences in SFCT have been previously reported in Caucasian and Middle Eastern patients using EDI-OCT and swept-source OCT (SS-OCT).[11,24] The disparity in ocular blood flow may contribute to the CT-observed asymmetry between the eyes. The right ophthalmic artery receives blood from the brachiocephalic trunk, which is closer to the left ventricle than the left common carotid artery, which forks off to form the left ophthalmic artery.[25,26] In the current investigation, SD-OCT was only applied to the subfoveal slabs. SS-OCT provides greater sclerochoroidal junction delineation than SD-OCT, so it may be superior for evaluating SFCT and CVI. In contrast, the evaluation of perifoveal regions in addition to foveal slabs in future studies can provide additional information regarding the normal distribution of SFCT/CVI in healthy individuals and inter-eye differences.

Limitations of the current study include relatively small sample size and the lack of inclusion of pediatric and younger patients. While this sample size provides valuable insights into the SFCT and vascularity index of healthy Iranian adults in our region, we acknowledge that it may not be directly generalizable to the entire Iranian population. Future research with larger and more diverse samples is warranted to confirm our findings and improve generalizability across different subgroups within the Iranian population. Participants may not represent all ethnicities in Iran. In addition, the RPE line and choroidoscleral border were determined manually, which may have introduced an error in determining the SFCT and CVI measurements. For more precise measurements of SFCT and CVI measurements, it is suggested that researchers use polarization-sensitive SS-OCT.

In conclusion, this is the first study assessing SFCT and CVI in the Iranian population. CVI was less variable than SFCT in a healthy population and can be considered a more robust parameter for evaluating choroidal structural alterations in different ophthalmic diseases.

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Conflicts of interest
There are no conflicts of interest.

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