# Choroidal Vascularity Index in Primary Open Angle Glaucoma

Primer Açık Açili Glokomda Koroid Vasküler İndeks

# Gozde Hondur<sup>1</sup>, Ahmet M Hondur<sup>2</sup>

<sup>1</sup>Ulucanlar Ophthalmology Training and Research Hospital, Ankara, Turkey <sup>2</sup>Gazi University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey

#### ABSTRACT

**Objective:** To study the choroidal vascularity index (CVI) and choroidal thickness changes in primary open-angle glaucoma (POAG) compared to healthy control eyes with the enhanced depth imaging (EDI) modality of an optical coherence tomography (OCT).

**Methods:** In this cross-sectional observational study, the CVI and the subfoveal choroidal thickness were assessed with EDI OCT and compared among 31 POAG cases and 25 healthy controls, which were age- and sex-matched. EDI OCT images were binarized into luminal area (LA) and stromal area. The CVI was defined as proportion of the luminal area to the total circumscribed choroidal area. The correlation between the visual field mean deviation (MD) value and choroidal parameters of the POAG cases were also evaluated.

**Results:** The eyes with POAG had lower mean CVI compared to the control eyes (p<0.00001) while the mean choroidal thickness values were mostly similar (p=0.94). The CVI values of the POAG eyes had significant correlation with the visual field MD values (r=0.51, p=0.01), while choroidal thickness values of the POAG eyes did not demonstrate such an association with the visual field MD values (r=0.14, p=0.51).

**Conclusion:** The lower CVI in POAG eyes compared to healthy controls and its significant correlation with the severity of glaucoma imply the role of choroidal vascularity in POAG pathogenesis.

**Keywords:** Primary open angle glaucoma; enhanced depth imaging; optical coherence tomography; subfoveal; choroidal thickness; choroidal vascularity index.

Received: 10.18.2020

Accepted: 02.01.2021

# ÖZET

**Amaç:** Primer açık açılı glokomda (PAAG) koroid kalınlığı ve koroid vaskülarite indeks (KVİ) değişikliklerinin sağlıklı kontrollerle, optik koherans tomografi (OKT) arttırılmış derinlik görüntüleme (ADG) modu ile karşılaştırılmasıdır.

Yöntem: Bu kesitsel gözlemsel çalışmada, koroid vaskülarite indeksi (KVİ) ve subfoveal koroid kalınlığı ADG mod OKT ile değerlendirildi. PAAG vakaları (n=31) ile yaş-cinsiyet eşleştirilmiş sağlıklı kontrol olguları (n=28) karşılaştırıldı. ADG mod OKT görüntüleri lümen ve stromal alanı gösterecek şekilde binarize edildi. KVİ, lümen alanının sınırları belirlenmiş total koroid alanına oranı olarak tanımlandı. PAAG'lı gözlerde, görme alanı ortalama sapma (MD) değerleri ile koroid parametreleri arasındaki korelasyon da değerlendirildi.

**Bulgular:** PAAG'lı gözlerde kontrol grubuna göre daha düşük ortalama KVİ değerleri saptanırken (p<0.00001), koroid kalınlığı iki grup arasında benzer bulundu (p=0.94). PAAG'lı gözlerin ortalama KVİ değerleri görme alanı MD değerleri ile anlamlı korelasyon gösterirken (r=0.51, p=0.01), koroid kalınlığı değerleri görme alanı MD değerleri ile anlamlı bir korelasyon göstermedi (r=0.035, p=0.84).

**Sonuç:** PAAG'lı gözlerde sağlıklı gözlere kıyasla izlenen düşük KVİ ve KVİ'nin hastalığın şiddetini gösteren MD ile anlamlı korelasyonu, koroid vaskülaritesinin PAAG patogenezinde rol oynayabileceğini düşündürmektedir.

Anahtar Sözcükler: Primer açık açılı glokom; arttırılmış derinlik görüntüleme; optik koherans tomografi; subfoveal; koroid kalınlığı; koroid vaskülarite indeksi

Geliş Tarihi: 18.10.2020

Kabul Tarihi: 01.02.2021

ORCID IDs: G.H. 0000-0002-3615-8884, A.M.H. 0000-0003-3955-6869

Address for Correspondence/Yazışma Adresi: Gözde Hondur, MD Ulucanlar Göz Eğitim Araştırma Hastanesi, Ulucanlar Caddesi No 59 06250, Altındağ Ankara, Turkey Email: gozdealtiparmak@yahoo.com

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doi:http://dx.doi.org/10.12996/gmj.2021.97

## INTRODUCTION

Glaucoma is characterized by progressive and irreversible degeneration of retinal ganglion cells resulting in structural alterations at the optic nerve head and an accompanying decrease in visual field sensitivity (1). Intraocular pressure (IOP) is the most important modifiable risk factor for glaucoma. Although the pathogenesis of glaucoma is not fully understood, there is growing evidence that vascular impairment has an important role in the development and the progression of the disease (2,3). Previous studies have demonstrated an association between glaucoma and impaired choroidal circulation (4,5).

The progress in ocular imaging technologies has provided clinicians with new methods to evaluate the structural and vascular characteristics of the choroid with greater detail. Particularly, the enhanced depth imaging (EDI) mode of the optical coherence tomography (OCT) has become a widely used method for imaging the choroid (6).

In terms of glaucoma, previous reports have demonstrated no change in the choroidal thickness in primary open-angle glaucoma (POAG) compared with healthy controls (7-9). However, measurement of choroidal thickness may not specify vascular damage, as the choroid is composed of both vasculature and stroma. Therefore, the measurement of choroidal thickness for evaluating the vascular status may be of limited value in glaucoma.

Choroidal vascularity index (CVI) has been introduced as a new method to assess choroidal vascular status (10).

As a technique evaluating the vascularity of the choroid, CVI may carry a potential for increasing our understanding of the role of the choroidal vascular changes in glaucoma pathogenesis. Hence, the present study is aimed at investigating the subfoveal CVI in eyes with POAG versus that of healthy controls and evaluating the correlation between choroidal parameters and severity of glaucomatous damage.

#### METHODS

#### Study participants

OCT images employed in this cross-sectional observational study were obtained from glaucoma patients and healthy subjects who agreed to participate after the nature of the tests was explained. All consecutive eligible subjects willing to participate were enrolled.

A complete medical history was taken from all the participants, all of whom underwent a comprehensive ophthalmological examination and testing including Goldmann applanation tonometry, gonioscopy, dilated fundus examination, retinal nerve fiber layer (RNFL) analysis on optical coherence tomography (OCT; Spectralis, Heidelberg Engineering GmbH, Heidelberg, Germany) and standard automated perimetry (Humphrey Visual Field Analyzer, 24-2 Swedish Interactive Threshold Algorithm (SITA) Standard strategy; Carl Zeiss Meditec Inc., Dublin, CA). Also, the central corneal thickness and axial length parameters were evaluated. One eye was randomly chosen if both eyes of a subject were eligible for the study.

The inclusion criteria for healthy subjects were a best corrected visual acuity of 20/30 or better, a spherical refractive error within +5 to -5 diopters (D), < 3 D of astigmatism, no media opacities that interfere with fundus imaging, normal clinical ocular findings with no evidence of retinal or optic nerve head pathologies, IOP of <21 mm Hg, open iridocorneal angles, intact RNFL, and normal visual field results, which was defined as a pattern standard deviation (PSD) within 95% confidence limits and a glaucoma hemifield test result within normal limits on a reliable 24-2 Swedish interactive thresholding algorithm.

The inclusion criteria for POAG was defined as a glaucomatous optic nerve appearance (neuroretinal rim thinning or notching), a gonioscopically open anterior chamber angle, RNFL thinning outside the 95% confidence interval of the normal distribution on OCT, and a glaucomatous visual field defect or an abnormal glaucoma hemifield test result that is outside the limits described above. Subjects were excluded if they had a history of previous ocular trauma or posterior segment intraocular surgery, conditions other than glaucoma that may affect the optic nerve structure or visual field testing, any retinal disease that may affect macular thickness such as diabetic macular edema, epiretinal membrane or age-related macular degeneration, systemic diseases such as diabetes mellitus or hypertension, or a visually significant cataract with a corrected visual acuity of less than 20/40.

#### EDI OCT Image Acquisition and Choroidal Thickness and CVI Assessment

OCT imaging was performed with the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) using the EDI mode. After mydriasis was attained and the patient appropriately positioned, the EDI-OCT scan of the foveal center was acquired.

The choroidal thickness was calculated from retinal pigment epithelium to the outer border of the choroid at the subfoveal area using the calipers provided in the software.

EDI OCT images were analyzed with the ImageJ software (Version 1.47, National Health Institute, Bethesda, MA) using the binarization protocol described by Agrawal and associates (10). After converting the image into 8 bit, the Niblack autolocal threshold tool was applied, which allows the demarcation of the choroidal stroma and its total vascular lumen. The binarized image was then transformed to the RGB format, and luminal areas were highlighted with the color thresholding tool (Figure 1). The total choroidal, luminal and stromal areas were then calculated within the central 1500µm. The fraction of the luminal area to the total choroidal area yielded the CVI. All the CVI analysis and measurements were performed separately by two blinded investigators.



**Figure 1. (A)** The enhanced depth imaging (EDI) optical coherence tomography (OCT) scan passing through the foveal center of each eye was selected. Total choroidal area, lumen area and stromal area were calculated in the central 1500µm. (**B**) The image was converted to 8 bits and thresholding was applied. (**C**) Each binarized image was then converted to an RGB image, and the luminal area was determined using the color thresholding tool.

#### Statistical Analysis

All statistical analyses were performed with the SPSS software (SPSS for Windows Version 20.0; SPSS Inc., Chica-go, IL). Chi-squared analysis test was used for the categorical variables while independent samples t-test was used to compare the mean age, IOP, axial length, central corneal thickness, choroidal thickness and CVI values of the 2 groups. A p value less than 0.05 was considered significant.

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Correlations between the choroidal thickness and the CVI values and the corresponding MD values of visual field were evaluated using Pearson regression analyses in glaucoma patients.

#### Ethical Approval

All investigations adhered to the tenets of the 1964 Declaration of Helsinki, and the study received approval from the Institutional Review Board and Ethics Committee (Ankara Education and Research Hospital Ethics Committee Approval Number=E-93471371-514.10). Informed consent was obtained from all the individual participants included in the study.

#### Table 1. Clinical and demographic data of the groups.

### RESULTS

Thirty-one eyes with POAG, and 25 eyes of healthy controls were evaluated in this study. There was no intergroup difference in terms of age, axial length and central corneal thickness. All patients in the study were Caucasians. The eyes with POAG were under anti-glaucomatous treatment, and there was no significant difference in the IOP values of the two groups at the time of the study. The patient demographics and clinical characteristics are summarized in Table 1.

	Controls	Primary Open Angle Glaucoma	p value		
Number of eyes	25	31			
Gender (F/M)	10/15	13/18	0.88*		
Age (Years)	67.7±9.0	68.3 <b>±6.3</b>	0.77**		
Axial length (mm)	23.41±0.98	23.08±1.43	0.40**		
Central corneal thickness (µm)	538±29	547±20	0.20**		
IOP(mmHg)	15.1±3	14.5±2.2	0.43**		
Mean deviation (dB)	n/a	8.46±8.2			

F/M: Female/male, mm: Millimetre, µm: Micrometre, dB: Decibel.

Data are presented as mean±standard deviation.

Statistical significance was calculated with the independent samples t-test \*\* and the chi square test\*.

Table 2 demonstrates the subfoveal choroidal parameters of the groups in detail. POAG eyes had markedly lower CVI values compared to the control eyes

(p<0.00001). However, POAG eyes had similar subfoveal choroidal thickness values compared to the control eyes. (Table 2).

Table 2. Choroidal parameters of the study groups.

	Primary Open Angle Glaucoma	Controls	p value
Choroidal Thickness	278.09±62.27	279.32±72.00	0.94
Choroidal Vascularity Index (CVI)	0.64±0.03	0.69±0.01	<0.00001

F/M: Female/male, mm: Millimetre,  $\mu$ m: Micrometre, dB: Decibel.

Data are presented as mean±standard deviation.

Statistical significance was calculated with the independent samples t-test \*\* and the chi square test\*.

The CVI values demonstrated significant correlation with visual field MD values in the POAG group (r=0.51, p=0.01), while the choroidal thickness values did not demonstrate any correlation with visual field MD values in the same group (r=0.14, p=0.53).

#### DISCUSSION

Various studies have reported that vascular factors and reduced ocular blood flow are associated with the pathogenesis of glaucoma (11-16). According to the vascular theory, the pathogenesis of glaucoma has been linked to the vascular insufficiency at the optic nerve head, especially the prelaminar area that is supplied from the choroid (17). However, the role of the choroid in the pathogenesis of glaucomatous optic neuropathy is not clearly identified (18). In the present study we aimed at augmenting our understanding of the potential role of the choroidal vascular alterations in glaucoma pathogenesis.

The introduction of EDI OCT has enabled non-invasive, quantitative and detailed evaluation of the choroid (19). Choroidal thickness has been the first surrogate marker for choroidal structural alterations on OCT. However previous

studies have not established a relationship between choroidal thickness and glaucoma (7-9), most probably resulting from the wide variation of the choroidal thickness and the various factors that affect the thickness. In addition, the choroidal thickness evaluation does not differentiate the changes between its vascular and stromal components. Hence, more recent studies have concentrated on evaluating the vascular and stromal components of the choroid separately (20-22). CVI assessment involves an image binarization technique to calculate the relative vascular component of the choroid (23). Agrawal and associates studied the variation in CVI in healthy eyes and presented that CVI was a superior marker for the assessment of choroidal disease than choroidal thickness (10).

In the present study, POAG eyes had lower subfoveal CVI values compared to age matched healthy control eyes. However subfoveal choroidal thickness values did not differ among POAG and control eyes, suggesting the lack of any relationship between the choroidal thickness and POAG. This finding was also in accordance with previous reports demonstrating no associations between choroidal thickness and POAG (7-9).

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We demonstrated a lower CVI despite mostly similar choroidal thickness values in POAG eyes compared with that of healthy controls. CVI may be more sensitive in representing the vascular impairment as it specifically analyses the vascular component, and the preservation of the choroidal stroma while its vascularity is being affected may limit the decrease in the choroidal thickness. The wide variation of the choroidal thickness and the various factors that affect it also may act as confounding factors.

Furthermore, in the present study, subfoveal CVI had significant correlations with corresponding visual field MD values in the POAG eyes, which supports not only diagnostic but also prognostic implications of studying the choroidal vascularity status.

Only a single study has reported reduced subfoveal CVI in eyes with open angle glaucoma compared with healthy eyes (24). Our results are consistent with this previous report. In addition, we demonstrated a correlation of the CVI with the visual field MD values, and hence with the disease severity. This implies the prognostic value of the choroidal vascularity status. On the other hand, the choroidal thickness values did not demonstrate any correlation with the visual field MD values in the same group.

The major strength of the present study was the strict matching of the groups for age, axial length, IOP, and central corneal thickness. Age, axial length, CCT are significantly associated with changes in the choroidal thickness in glaucoma suspects and glaucoma patients (25). Contrariwise, CVI appeared to be a strong marker for gauging the vascular status of the choroid. In addition, it is known to be mostly unaffected or affected to a lesser degree by most physiological variables, such as age, refractive error, IOP, axial length, arterial blood pressure, and diurnally (26).

Though, the present study is not without limitations. Its cross-sectional design, which precluded the longitudinal follow-up of glaucoma patients and analysis of disease progression, may be considered as the major limitation. In addition, although not validated yet, different intraocular pressure-lowering drops may have different effects on the choroidal vascularity.

In conclusion, our study demonstrated lower mean CVI values in eyes with POAG versus that of healthy subjects. The results support the role of choroidal vascular insufficiency in the pathogenesis of POAG. Lower CVI values along with correlation of the CVI values with the visual field MD values in POAG eyes represents possible choroidal involvement in POAG, with an ischemic factor that could either be a trigger or effect of the disease. Conversely, similar choroidal thickness values in eyes with POAG compared with that of healthy controls imply the lack of both a correlation and any use of choroidal thickness as an imaging biomarker in POAG.

#### Conflict of interest

No conflict of interest was declared by the authors.

#### REFERENCES

- 1. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. JAMA 2014; 311(18): 1901-1911.
- Flammer J, Orgul S, Costa VP, Orzalesi N, Krieglstein GK, Serra LM, et al. The impact of ocular blood flow in glaucoma. Prog Retin Eye Res 2002; 21(4): 359-393.
- Grieshaber MC, Mozaffarieh M, Flammer J. What is the link between vascular dysregulation and glaucoma? Surv Ophthalmol 2007; 52 Suppl 2: 144-154.
- Samra WA, Pournaras C, Riva C, Emarah M. Choroidal hemodynamic in myopic patients with and without primary open-angle glaucoma. Acta Ophthalmol. 2013; 91:371–375.
- Duijm HF, van den Berg TJ, Greve EL. Choroidal haemodynamics in glaucoma. Br J Ophthalmol 1997; 81:735–742.
- Laviers H, Zambarakji H. Enhanced depth imaging-OCT of the choroid: a review of the current literature. Graefes Arch Clin Exp Ophthalmol 2014;252(12):1871-1883.
- Wang W, Zhang X. Choroidal thickness and primary open-angle glaucoma: a cross-sectional study and meta-analysis. Invest Ophthalmol Vis Sci 2014 Aug 28;55(9):6007-14.

- Mwanza JC, Hochberg JT, Banitt MR, Feuer WJ, Budenz DL. Lack of association between glaucoma and macular choroidal thickness measured with enhanced depth-imaging optical coherence tomography. Invest Ophthalmol Vis Sci 2011 May 18; 52(6): 3430-5.
- **9.** Park HY, Lee NY, Shin HY, Park CK. Analysis of macular and peripapillary choroidal thickness in glaucoma patients by enhanced depth imaging optical coherence tomography. J Glaucoma 2014 Apr-May; 23(4):225-31.
- Agrawal R, Gupta P, Tan KA, Cheung CM, Wong TY, Cheng CY. Choroidal vascularity index as a measure of vascular status of the choroid: measurements in healthy eyes from a population-based study. Sci Rep 2016; 6: 21090.
- Venugopal JP, Rao HL, Weinreb RN, Pradhan ZS, Dasari S, Riyazuddin M, et al. Repeatability of vessel density measurements of optical coherence tomography angiography in normal and glaucoma eyes. Br J Ophthalmol 2018; 102(3): 352-357.
- **12.** Wolf S, Arend O, Sponsel WE, Schulte K, Cantor LB, Reim M. Retinal hemodynamics using scanning laser ophthalmoscopy and hemorheology in chronic open-angle glaucoma. Ophthalmology 1993; 100:1561-1566.
- Hamard P, Hamard H, Dufaux J. Blood flow rate in the microvasculature of the optic nerve head in primary open angle glaucoma. A new approach. Surv Ophthalmol 1994; 38: 87-93.
- 14. Michelson G, Langhans MJ, Harazny J, Dichtl A. Visual field defect and perfusion of the juxtapapillary retina and the neuroretinal rim area in primary open-angle glaucoma. Graefes Arch Clin Exp Ophthalmol 1998; 236: 80-85.
- 15. O'Brart DP, de Souza Lima M, Bartsch DU, Freeman W, Weinreb RN. Indocyanine green angiography of the peripapillary region in glaucomatous eyes by confocal scanning laser ophthalmoscopy. Am J Ophthalmol 1997;123: 657-666.
- Huber K, Plane N, Remky A, Arend O. Comparison of colour Doppler imaging and retinal scanning laser fluorescein angiography in healthy volunteers and normal pressure glaucoma patients. Acta Ophthalmol Scand 2004; 82: 426-431.
- **17.** Hayreh SS. The blood supply of the optic nerve head and the evaluation of it myth and reality. Prog Retin Eye Res 2001 Sep; 20(5): 563-93.
- Banitt M. The choroid in glaucoma. Curr Opin Ophthalmol 2013 Mar;24(2):125-9.
- **19.** Spaide RF, Koizumi H, Pozzoni MC. Enhanced depth imaging spectral-domain optical coherence tomography. Am J Ophthalmol 2008; 146: 496–500.
- 20. Branchini LA, Adhi M, Regatieri CV, Nandakumar N, Liu JJ, Laver N, et al. Analysis of choroidal morphologic features and vasculature in healthy eyes using spectral-domain optical coherence tomography. Ophthalmology 2013; 120: 1901–1908.
- 21. Sonoda S, Sakamoto T, Yamashita T, Shirasawa M, Uchino E, Terasaki H et al. Choroidal structure in normal eyes and after photodynamic therapy determined by binarization of optical coherence tomographic images. Invest Ophthalmol Vis Sci 2014; 55: 3893–3898.
- 22. Sonoda S, Sakamoto T, Yamashita T, Uchino E, Kawano H, Yoshihara N, et al. Luminal and stromal areas of choroid determined by binarization method of optical coherence tomographic images. Am J Ophthalmol 2015; 159:1123-1131.e1.
- 23. Agrawal R, Salman M, Tan KA, Karampelas M, Sim DA, Keane PA, et al. Choroidal vascularity index (CVI)-a novel optical coherence tomography parameter for monitoring patients with panuveitis? PLoS One 2016;11: e0146344.
- **24.** Park Y, Cho KJ. Choroidal vascular index in patients with open angle glaucoma and preperimetric glaucoma. PLoS One 2019; 14(3): e0213336.
- 25. Maul EA, Friedman DS, Chang DS, Boland MV, Ramulu PY, Jampel HD, et al. Choroidal thickness measured by spectral domain optical coherence tomography: factors affecting thickness in glaucoma patients. Ophthalmology 2011; 118: 1571–1579.
- 26. Agrawal R, Ding J, Sen P, Rousselot A, Chan A, Nivison-Smith L, et al. Exploring choroidal angioarchitecture in health and disease using choroidal vascularity index. Prog Retin Eye Res 2020 Jul;77:100829.