Assessment of primary open-angle glaucoma peripapillary and macular choroidal area using enhanced depth imaging optical coherence tomography

Hirokazu Kojima¹, Kazuyuki Hirooka²*, Eri Nitta¹, Shozo Sonoda³, Taiji Sakamoto³, Yoshiaki Kiuchi²

¹ Department of Ophthalmology, Kagawa University Faculty of Medicine, Kagawa, Japan, ² Department of Ophthalmology and Visual Science, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan, ³ Department of Ophthalmology, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan

* khirooka9@gmail.com

Abstract

Purpose

The current study investigated differences in the peripapillary and macular choroidal areas between patients with primary open-angle glaucoma (POAG) and healthy controls because the choroid may potentially play a role in glaucoma pathophysiology.

Methods

We assessed 57 healthy controls and 42 POAG patients in a cross-sectional comparative study. We used enhanced depth imaging optical coherence tomography (EDI-OCT) and then converted the luminal and interstitial areas to binary images using the Niblack method to obtain peripapillary and macular choroidal images. The relationship between the choroidal area and demographic and ocular characteristics were determined with univariate and multivariate linear regression analysis.

Results

Regarding the peripapillary choroidal area, no significant differences were noted between healthy controls and POAG patients (1,836,336 ± 605,617 μm² vs. 1,775,566 ± 477,317 μm², respectively, \( P = 0.60 \)). There were also no differences found for the macular choroidal area (controls: 347,220 ± 115,409 μm², patients: 342,193 ± 104,356 μm², \( P = 0.83 \)). Multivariate regression analysis in the POAG patients revealed there was a significant relationship between the macular choroidal area and age (\( \beta = -0.525, P = 0.002 \)) and axial length (\( \beta = -0.458, P = 0.005 \)). In contrast, no correlation was found between peripapillary choroidal areas and various attributes in the POAG patients.
Conclusions
EDI-OCT showed no differences in the peripapillary or macular choroidal area in healthy individuals compared to POAG patients.

Introduction
The most abundant blood vessel layer in the eye is the choroid, which has the most abundant blood flow in the body per unit tissue weight.[1] The microvasculature of the peripapillary choroid is an important consideration in glaucoma because short posterior ciliary arteries supply the choroid and the optic nerve head. Thus, understanding the pathophysiological mechanisms of glaucoma requires assessment of the choroid.

New techniques have been introduced, including enhanced depth imaging (EDI) spectral domain optical coherence tomography (OCT), which allow cross-sectional imaging of the choroid.[2] Several studies have used these methods and described relationships between the thickness of the choroid and glaucoma. Some reports have shown no differences in choroidal thickness in healthy compared to glaucoma patients,[3–6] whereas others have shown a thinner choroid in glaucoma patients.[7–9] These previous studies measured the thickness of the choroid in a small area (at 1.7 mm superior, temporal, inferior, and nasal to the optic disc center and at 1- and 3-mm nasal, temporal, superior, and inferior to the fovea). In our previous studies, we assessed a 1,500-μm wide macular choroid and a 1.7-mm area of the peripapillary choroid near the middle of the optic nerve disc[10–12], thus allowing us to obtain more information about the choroid.

Intraocular pressure (IOP) is considered the main risk factor for primary open-angle glaucoma (POAG). However, in normal-tension glaucoma (NTG), increased IOP is less important.[13] Thus, factors other than the IOP should also be considered when evaluating glaucoma. As the choroid has a significant role with regard to the ocular blood flow, it is thought to be important in the pathophysiology of glaucoma.[14] Our previous study showed a smaller peripapillary choroidal area in patients with NTG.[11] Here we compared the area of the peripapillary and macular choroid in healthy vs. POAG eyes.

Materials and methods
Patients
This cross-sectional comparative study evaluated participants who underwent testing at Kagawa University Hospital between July 2018 and March 2019. The study was conducted according to the principles of the Declaration of Helsinki. Each patient was provided a detailed explanation of the study and gave written informed consent. The Kagawa University Faculty of Medicine Institutional Review Board approved the study’s protocol.

All patients completed a full ophthalmic examination in which the central corneal thickness (CCT), central and peripheral fields, gonioscopy, slit lamp, and visual acuity were assessed with refraction. Age- and axial length-matched healthy control volunteers underwent the same measurements. Patients were enrolled only if they had a spherical error between +4.0 and −6.0 diopters (D) and a cylinder within ±2.0 D. Eyes with glaucoma were considered those with glaucomatous optic disc changes (thinning of the neuroretinal rim, notching, or a defect in the retinal nerve fiber layer) and visual field loss. Glaucomatous visual field loss was defined as at least two consecutive baseline hemifield tests were outside the normal limits. This definition
included at least three contiguous test points in the same hemifield with a pattern deviation plot at $P < 1\%$, and at least one test point at $P < 0.5\%$. A POAG diagnosis was defined as an untreated IOP of $>21$ mmHg. We used the same inclusion and exclusion criteria reported in a previous study.[11] One inclusion criterion was open angles. Patients with a history of retinal diseases, poor image quality due to unstable fixation, severe cataracts, or a history of previous laser therapy were excluded. The same researcher performed all EDI-OCT examinations. Only one eye, typically the right eye, was examined in each patient to exclude individual variations. If the right eye did not meet the inclusion criteria, we examined the left eye.

**EDI-OCT**

The Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany) with the EDI-OCT technique was used to capture the macular or peripapillary choroidal images.[10–12] All measurements were obtained between 13:00 and 15:00 hours. All eyes were examined without mydriasis. The macular region images were captured using seven horizontal lines of $30 \times 10^\circ$ through the center of the fovea. The peripapillary region images were obtained using a $360^\circ$ circle that was $3.4$ mm in diameter that was centered on the optic disc. The best quality image from at least three scans was used for assessment. Choroidal thickness was considered to be the area between the outer portion of the hyperreflective line that corresponded to the retinal pigment epithelium and the inner surface of the sclera. The manual segmentation function was used because Spectralis OCT does not provide an algorithm for automatic segmentation of the choroid.

**Binarization of the choroid EDI-OCT images**

The best EDI-OCT images were recorded, masked, and displayed on a computer screen. One author (HK) examined each image. The choroidal area in each EDI-OCT image was binarized using the modified Niblack method.[15] Briefly, the area of the macular choroid that was $1,500 \mu m$ wide and that extended vertically (Fig 1A and 1B) in EDI-OCT images was first assessed using ImageJ software (version 1.47, NIH, Bethesda, MD).[10–12] The examined region included a $1.7$-mm area around the optic nerve disc center (Fig 1C and 1D) that ranged from the retinal pigment epithelium to the chorioscleral border.[10–12] Areas were delineated with ImageJ ROI Manager. We averaged the reflectivities of the lumens of three randomly selected choroidal vessels with lumens $>100 \mu m$ that were selected using the Oval Selection Tool on the ImageJ tool bar. To reduce the noise in the OCT image, this average reflectivity was defined as the minimum value. The image was converted, adjusted to 8 bits using the Niblack Auto Local Threshold program, and then the binarized image was converted to a RGB image because of technical requirements for binarization and the automated calculations performed by ImageJ. The Threshold Tool was used to identify the hyporeflective area, with dark and light pixels considered hyporeflective and hyperreflective areas, respectively. Information was added about the relationship between the distance on the fundus and the pitch of the pixels in the EDI-OCT images, which depend on the axial length, and then the hyperreflective and hyporeflective areas were automatically calculated. Light and dark pixels were considered the interstitial choroid and the luminal area, respectively.

**Statistical analysis**

The sample size was chosen according to our previous report[10] and was calculated by assuming a 10% variation in the peripapillary choroidal area between the POAG and healthy group and a 1:1 ratio of glaucomatous to normal eyes. The sample size needed was 33 per group for a predictive power of 90%.
JMP software version 14 (SAS Inc., Cary, NC) was used for statistical analyses. The independent Student’s \( t \)-test was performed to assess differences in age, IOP, systolic blood pressure (SBP), diastolic blood pressure (DBP), ocular perfusion pressure (OPP), CCT, and axial length. Differences in the categorical parameters were assessed using the \( \chi^2 \) test. OPP was calculated as \( \text{OPP} = \frac{2}{3}[\text{DBP} + \frac{1}{3}(\text{SBP} - \text{DBP})] - \text{IOP} \). Univariate and multivariate linear regression was used to assess the relationship between the choroidal area and different parameters including age, axial length, CCT, IOP, DBP, and OPP in the POAG and healthy groups. Variables with \( P < 0.2 \) in the univariate regression were included in the multivariate regression. \( P < 0.05 \) was considered statistically significant. All data are shown as the mean ± standard deviation (SD).

**Results**

Clinical characteristics of the enrolled subjects are presented in Table 1. The mean age of the healthy controls and POAG patients was 64.9 ± 11.9 years (range, 40–85 years) and 67.6 ± 10.1 years (range, 34–86 years), respectively (\( P = 0.36 \)). No significant differences were observed for gender (\( P = 0.16 \)), IOP (\( P = 0.06 \)), axial length (\( P = 0.07 \)), or OPP (\( P = 0.85 \)).

Mean peripapillary choroidal areas were 1,836,336 ± 605,617 \( \mu \text{m}^2 \) and 1,775,566 ± 477,317 \( \mu \text{m}^2 \) in the healthy controls and POAG patients, respectively (\( P = 0.60 \)) (Table 2). Peripapillary luminal and interstitial areas were 1,029,898 ± 430,908 \( \mu \text{m}^2 \) and 806,437 ± 183,512 \( \mu \text{m}^2 \) in the healthy controls and 994,971 ± 330,883 \( \mu \text{m}^2 \) (\( P = 0.67 \)) and 780,595 ± 164,300 \( \mu \text{m}^2 \) (\( P = 0.48 \))
in POAG patients, respectively (Table 2). Macular choroidal, luminal, and interstitial areas were 347,220 ± 115,409 μm², 226,191 ± 81,621 μm², and 121,029 ± 36,899 μm² in the healthy controls and 342,193 ± 104,356 μm², 225,314 ± 72,722 μm², and 116,878 ± 35,532 in POAG patients, respectively (Table 2). We found no significant differences between the healthy controls and POAG patients.

Subsequently, we then divided the POAG patients into two groups, the uncontrolled/progressive and the controlled group. Mean peripapillary choroidal areas were 1,731,441 ± 424,960 μm² (P = 0.63, Dunnett t-test, as compared to healthy controls) in the uncontrolled/progressive POAG patients (n = 32) and 1,916,767 ± 641,953 μm² (P = 0.89) in the controlled POAG patients (n = 10). Macular choroidal areas were 327,789 ± 94,926 μm² (P = 0.67) in the uncontrolled/progressive POAG patients and 388,282 ± 129,172 μm² (P = 0.48) in the controlled POAG patients.

Univariate regression revealed a significant negative relationship with age for the peripapillary choroidal area of the healthy controls (β = −0.483, P = 0.0002). Univariate regression additionally indicated a significant association with age (Healthy: β = −0.272, P = 0.04, POAG: β = −0.312, P = 0.04) for the macular choroidal area of the healthy controls and POAG patients (Table 3). Multivariate regression analysis demonstrated a significant relationship for age (β = −0.419, P = 0.002), axial length (β = −0.512, P = 0.0002), and CCT (β = 0.303, P = 0.01) with the macular choroidal area in healthy controls (Table 4). In addition, we identified a significant

| Table 1. Clinical characteristics of healthy controls and primary open-angle glaucoma patients. |
|----------------------------------|-----------|-----------|-----------|
| Age (y)                          | Healthy   | POAG      | P value   |
| Gender (M/F)                     | 64.9 ± 11.9 | 67.6 ± 10.1 | 0.36      |
| IOP (mmHg)                       | 14.9 ± 3.3  | 16.1 ± 2.9  | 0.06      |
| Axial length (mm)                | 24.2 ± 1.7  | 24.8 ± 1.8  | 0.07      |
| Central corneal thickness (μm)  | 526.2 ± 38.7 | 528.9 ± 53.9 | 0.78      |
| Ocular perfusion pressure (mmHg) | 47.3 ± 7.2   | 47.6 ± 7.6   | 0.85      |
| Initial systemic blood pressure (mmHg) | 127.8 ± 15.7 | 129.4 ± 16.8 | 0.63      |
| Systolic                         | 76.0 ± 11.7  | 78.6 ± 11.1 | 0.27      |
| Diastolic                        | 9 (15.8)    | 8 (19.0)    | 0.67      |
| Hypertension (%)                 | 27 (47.4)   | 16 (38.1)   | 0.36      |
| Glaucoma history                 |            |            |           |
| Mean deviation (dB)              | -15.41 ± 7.41 |            |   |
| No. of glaucoma medications      | 3.3 ± 0.9   |            |           |
| IOP at first visit (mmHg)        | 18.6 ± 4.9  |            |           |

POAG; primary open-angle glaucoma, M; male, F; female, IOP; intraocular pressure

https://doi.org/10.1371/journal.pone.0231214.t001

| Table 2. Choroidal area observed in EDI-OCT images. |
|----------------------------------|-----------|-----------|-----------|
| Peripapillary choroidal area     | Healthy   | POAG      | P value   |
| Total area (μm²)                 | 1836336 ± 605617 | 1775566 ± 477317 | 0.60      |
| Luminal area (μm²)               | 1029898 ± 439098 | 994971 ± 330883  | 0.67      |
| Interstitial area (μm²)          | 806437 ± 183512 | 780595 ± 164300  | 0.48      |
| Macular choroidal area           | Healthy   | POAG      | P value   |
| Total area (μm²)                 | 347220 ± 115409 | 342193 ± 104356 | 0.83      |
| Luminal area (μm²)               | 226191 ± 81621  | 225314 ± 72722  | 0.96      |
| Interstitial area (μm²)          | 121029 ± 36899  | 116878 ± 35532  | 0.58      |

POAG; primary open-angle glaucoma

https://doi.org/10.1371/journal.pone.0231214.t002
relationship between the macular choroidal area and age ($\beta = -0.525, P = 0.002$) and axial length ($\beta = -0.458, P = 0.005$) in the POAG patients. Univariate regression revealed a significant negative relationship with age for the peripapillary luminal or interstitial area of the healthy controls (luminal: $\beta = -0.460, P = 0.0004$, interstitial: $\beta = -0.515, P < 0.0001$, Tables 5 and 6). Multivariate regression analysis indicated that there was a significant relationship for age and axial length with the macular choroidal luminal area in the healthy controls and POAG patients (Table 7). Furthermore, multivariate regression analysis also demonstrated that there was a significant relationship for age, axial length and CCT with the macular choroidal interstitial area in healthy controls and for age with the macular choroidal interstitial area in the POAG patients (Table 8).

**Discussion**

Here we assessed the peripapillary and macular choroidal area in POAG patients compared to healthy controls. In NTG patients, we recently reported decreases in the peripapillary choroidal area,[11] suggesting that the peripapillary choroidal area is crucial to the pathogenesis of NTG.

NTG and POAG fall on a continuum of open-angle glaucoma. The main difference is that a sufficiently high IOP is the most important risk factor in POAG, and other factors in addition to IOP play an important role in NTG. Therefore, understanding the difference in pathology between NTG and POAG is important. NTG and POAG should be considered separately in studies of the pathology of glaucoma. Most OCT studies found no difference in the thickness of the peripapillary choroid between glaucoma patients and healthy controls.[3,4,16–19]
However, three studies[3,17,18] examined high-tension glaucoma patients, and one study[18] examined NTG patients. One study[4] included patients with both POAG and primary angle closure glaucoma (PACG), and another[16] did not report the glaucoma type. Some OCT studies showed a significantly thinner peripapillary choroid in glaucoma compared to healthy eyes.[7–9] Two studies[7,8] examined patients with NTG, and one[9] examined 114 NTG patients and 20 POAG patients. Thus, the study assessing NTG patients showed a significantly thinner peripapillary choroid in these patients. We recently found a significant difference in the peripapillary choroidal area between healthy controls and NTG patients, even though the macular choroidal area was similar in these groups.[11] In our present study, we did not find a difference in the peripapillary choroidal area in healthy controls compared to POAG patients. When we analyzed a direct POAG vs NTG, there was no significant difference in peripapillary choroidal area (1,775,566 ± 477,317 μm² vs 1,606,448 ± 418,214 μm², P = 0.11). Probably number of NTG patients were not enough (n = 35). The choroid supplies nearly three quarters of the eye’s circulating blood as well as nutrients to the outer retina and optic nerve head, especially the prelaminar region, which is involved in death of retinal ganglion cells in patients

Table 5. Univariate regression analysis of choroidal luminal area with associated factors.

|                      | Healthy | POAG | Healthy | POAG |
|----------------------|---------|------|---------|------|
| Peripapillary luminal area |         |      |         |      |
| Age                  | -0.460  | 0.0004 | -0.275  | 0.08 |
| Axial length         | -0.052  | 0.70  | -0.168  | 0.29 |
| CCT                  | -0.037  | 0.79  | -0.066  | 0.68 |
| IOP                  | 0.105   | 0.44  | 0.059   | 0.71 |
| OPP                  | -0.027  | 0.85  | 0.137   | 0.39 |
| BP                   |         |       |         |      |
| Systolic             | -0.043  | 0.75  | 0.182   | 0.25 |
| Diastolic            | 0.059   | 0.67  | 0.110   | 0.49 |
| Macular luminal area  |         |      |         |      |
| Age                  | -0.460  | 0.0004 | -0.275  | 0.08 |
| Axial length         | -0.052  | 0.70  | -0.168  | 0.29 |
| CCT                  | -0.037  | 0.79  | -0.066  | 0.68 |
| IOP                  | 0.105   | 0.44  | 0.059   | 0.71 |
| OPP                  | -0.027  | 0.85  | 0.137   | 0.39 |
| BP                   |         |       |         |      |
| Systolic             | -0.090  | 0.51  | 0.125   | 0.43 |
| Diastolic            | 0.072   | 0.60  | 0.072   | 0.65 |

POAG; Primary open-angle glaucoma, CCT; Central corneal thickness, IOP; Intraocular pressure, OPP; Ocular perfusion pressure
BP; Blood pressure

https://doi.org/10.1371/journal.pone.0231214.t005

Table 6. Univariate regression analysis of choroidal interstitial area with associated factors.

|                      | Healthy | POAG | Healthy | POAG |
|----------------------|---------|------|---------|------|
| Peripapillary interstitial area |         |      |         |      |
| Age                  | -0.515  | <0.0001 | -0.196  | 0.21 |
| Axial length         | 0.072   | 0.60  | -0.037  | 0.82 |
| CCT                  | -0.070  | 0.61  | 0.049   | 0.76 |
| IOP                  | 0.045   | 0.74  | 0.056   | 0.73 |
| OPP                  | -0.012  | 0.93  | 0.086   | 0.59 |
| BP                   |         |       |         |      |
| Systolic             | -0.090  | 0.51  | 0.125   | 0.43 |
| Diastolic            | 0.072   | 0.60  | 0.072   | 0.65 |
| Macular interstitial area |         |      |         |      |
| Age                  | -0.515  | <0.0001 | -0.196  | 0.21 |
| Axial length         | 0.072   | 0.60  | -0.037  | 0.82 |
| CCT                  | -0.070  | 0.61  | 0.049   | 0.76 |
| IOP                  | 0.045   | 0.74  | 0.056   | 0.73 |
| OPP                  | -0.012  | 0.93  | 0.086   | 0.59 |
| BP                   |         |       |         |      |
| Systolic             | -0.090  | 0.51  | 0.125   | 0.43 |
| Diastolic            | 0.072   | 0.60  | 0.072   | 0.65 |

POAG; Primary open-angle glaucoma, CCT; Central corneal thickness, IOP; Intraocular pressure, OPP; Ocular perfusion pressure
BP; Blood pressure

https://doi.org/10.1371/journal.pone.0231214.t006
The peripapillary choroidal area may play a more important role in glaucoma than the macular choroidal area because the former supplies blood to the optic nerve. Thus, the crucial difference in the pathology between POAG and NTG may be associated with the optic nerve blood supply.

We did not find an association between age and the peripapillary choroidal area in POAG patients, but a negative correlation was found in healthy controls. There was a significantly thinner peripapillary choroidal thickness in patients with glaucoma who had sclerotic optic disc damage as compared to that observed in patients with focal or diffuse optic disc damage or the healthy controls.[21] We assume that the presence of sclerotic optic disc damage in the POAG patients was related to the lack of an association observed between the age and the peripapillary choroidal area.

Macular choroidal area, except macular choroidal interstitial area, was correlated with age and axial length in POAG patients and healthy controls, which agrees with findings in most previous choroidal thickness studies.[4–6,9,22,23] Therefore, it is essential that both age and axial length are taken into account when choroidal area (thickness) is evaluated.

Our current study has some limitations. First, we had to identify Bruch’s membrane and the inner scleral border manually, because no OCT software can perform automated segmentation. Second, all glaucoma patients had a history of receiving anti-glaucoma drugs, which may impact choroidal thickness. Anti-glaucoma drugs can increase the subfoveal choroidal thickness in POAG patients.[24] However, here we only measured choroidal thickness in the subfoveal region and the parafoveal area; we did not assess peripapillary choroidal thickness, which may be associated with glaucoma.

In conclusion, healthy and POAG patients have similar peripapillary and macular choroidal areas as determined with EDI-OCT.

### Supporting information

**S1 Data.**

(XLSX)
Acknowledgments

The authors thank FORTE for the professional service that edited our manuscript.

Author Contributions

Conceptualization: Kazuyuki Hirooka.

Data curation: Hirokazu Kojima.

Formal analysis: Hirokazu Kojima.

Project administration: Kazuyuki Hirooka.

Software: Shozo Sonoda, Taiji Sakamoto.

Writing – original draft: Kazuyuki Hirooka.

Writing – review & editing: Hirokazu Kojima, Eri Nitta, Yoshiaki Kiuchi.

References

1. 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. https://doi.org/10.1016/j.ophtha.2013.01.066 PMID: 23664466

2. Spaide RK, Koizumi H, Pozzoni MC. Enhanced depth imaging spectral-domain optical coherence tomography. Am J Ophthalmol 2008; 146: 496–500. https://doi.org/10.1016/j.ajo.2008.05.032 PMID: 18639219

3. Ehrlich JR, Peterson J, Parilitsis G, Kay KY, Kiss S, Radcliffe NM. Peripapillary choroidal thickness in glaucoma measured with optical coherence tomography. Exp Eye Res 2011; 92: 189–194. https://doi.org/10.1016/j.exer.2011.01.002 PMID: 21232535

4. Maul EA, Friedman DS, Chang DS, Boland NV, 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. https://doi.org/10.1016/j.ophtha.2011.01.016 PMID: 21492939

5. 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; 52: 3430–3435. https://doi.org/10.1167/iovs.10-6600 PMID: 21357398

6. Mwanza JC, Sayyad FE, Budenz DL. Choroidal thickness in unilateral advanced glaucoma. Invest Ophthalmol Vis Sci 2012; 53: 6695–6701. https://doi.org/10.1167/iovs.12-10388 PMID: 22956612

7. Usui S, Ikuno Y, Miki A, Matsushita K, Yasuno Y, Nishida K. Evaluation of the choroidal thickness using high-penetration optical coherence tomography with long wavelength in high myopic normal-tension glaucoma. Am J Ophthalmol 2012; 153: 10–16. https://doi.org/10.1016/j.ajo.2011.05.037 PMID: 21864827

8. Hirooka K, Tenkumo K, Fujiwara A, Baba T, Sato S, Shiraga F. Evaluation of peripapillary choroidal thickness in patients with normal-tension glaucoma. BMC Ophthalmol 2012 Jul 28; 12:29. https://doi.org/10.1186/1471-2415-12-29 PMID: 22839368

9. Song YJ, Kim YK, Jeoung JW, Park KH. Assessment of open-angle glaucoma peripapillary and macular choroidal thickness using swept-source optical coherence tomography (SS-OCT). PLoS One 2016 Jun 16; 11(6):e0157333. https://doi.org/10.1371/journal.pone.0157333 PMID: 27309734

10. Kojima H, Hirooka K, Nitta E, Ukegawa K, Sonoda S, Sakamoto T. Changes in choroidal area after intraocular pressure reduction following trabeculectomy. PLoS One 2018 Aug 22; 13(8):e0201973. https://doi.org/10.1371/journal.pone.0201973 PMID: 30133501

11. Kojima H, Hirooka K, Nitta E, Sonoda S, Sakamoto T. Peripapillary and macular choroidal area in patients with normal-tension glaucoma. PLoS One 2018 Sep 13; 13(9):e0204183. https://doi.org/10.1371/journal.pone.0204183 PMID: 30212565

12. Kojima H, Hirooka K, Sonoda S, Sakamoto T, Kiuchi Y. Changes in choroidal area following trabeculectomy: long-term effect of intraocular pressure reduction. PLoS One 2019 Mar 20; 14(3):e0209145. https://doi.org/10.1371/journal.pone.0209145 PMID: 30893300
13. Shields MB. Normal-tension glaucoma: is it different from primary open-angle glaucoma? Cur Opin Ophthalmol 2008; 19:85–88.

14. Flammer J, Örgül S, Costa VP, Orzalesi N, Kriegstein GK, Serra LM, et al. The impact of ocular blood flow in glaucoma. Prog Retin Eye Res 2002; 21:359–393. https://doi.org/10.1016/s1350-9462(02)00008-3 PMID: 12150988

15. 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 optic coherence tomography images. Invest Ophthalmol Vis Sci 2014; 55: 3893–3898. https://doi.org/10.1167/iovs.14-14447 PMID: 24894395

16. Zhang C, Tatham AJ, Medeiros FA, Zangwill LM, Yang Z, Weinreb RN. Assessment of choroidal thickness in healthy and glaucomatous eyes using swept source optical coherence tomography. PLoS One 2014 Oct 8; 9(10):e109683. https://doi.org/10.1371/journal.pone.0109683 PMID: 25295876

17. Li L, Bian A, Zhou Q, Mao J. Peripapillary choroidal thickness in both eyes of glaucoma patients with unilateral visual field loss. Am J Ophthalmol 2013; 156: 1277–1284. https://doi.org/10.1016/j.ajo.2013.07.011 PMID: 24011520

18. Hosseini H, Nilforushan N, Moghimi S, Bitrian E, Riddle J, Lee GY, et al. Peripapillary and macular choroidal thickness in glaucoma. J Ophthalmic Vis Res 2014; 9: 154–161. PMID: 25279115

19. Suh W, Cho HK, Kee C. Evaluation of peripapillary choroidal thickness in unilateral normal-tension glaucoma. Jpn J Ophthalmol 2014; 58:62–67.

20. Cioffi GA, Wang L, Fortune B, Cull G, Dong J, Bui B, et al. Chronic ischemia induces regional axonal damage in experimental primate optic neuropathy. Arch ophthalmol 2004; 122: 1517–1525. https://doi.org/10.1001/archophth.122.10.1517 PMID: 15477464

21. Roberts KF, Artes PH, O'Leary N, Reis AS, Sharpe GP, Hutchison DM, et al. Peripapillary choroidal thickness in healthy controls and patients with focal, diffuse, and sclerotic glaucomatous optic disc damage. Arch Ophthalmol 2012; 130: 980–986. https://doi.org/10.1001/archophthalmol.2012.371 PMID: 22491392

22. Ikuno Y, Kawaguchi K, Nouchi T, Yasuno Y. Choroidal thickness in healthy Japanese subjects. Invest Ophthalmol Vis Sci 2010; 51: 2173–2176. https://doi.org/10.1167/iovs.09-4383 PMID: 19892874

23. Hirata M, Tsujikawa A, Matsumoto A, Hangai M, Ooto S, Yamashiro K, et al. Macular choroidal thickness and volume in normal subjects measured by swept-source optical coherence tomography. Invest ophthalmol Vis Sci 2011; 52: 4971–4978. https://doi.org/10.1167/iovs.11-7729 PMID: 21622704

24. Bayraktar S, Cebeci Z, Içgi B, Kasali K. The effect of glaucoma medication on choroidal thickness measured with enhanced depth-imaging optical coherence tomography. Med Hypothesis Discov Innov Ophthalmol 2019; 8: 44–51. PMID: 30923723