Factors Influencing Optical Coherence Tomography Peripapillary Choroidal Thickness: A Multicenter Study

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PURPOSE. To quantify peripapillary choroidal thickness (PCT) and the factors that influence it in healthy participants who represent the racial and ethnic composition of the U.S. population.

METHODS. A total of 362 healthy participants underwent optical coherence tomography (OCT) enhanced depth imaging of the optic nerve head with a 24 radial B-scan pattern aligned to the fovea to Bruch’s membrane opening axis. Bruch’s membrane, anterior scleral canal opening (ASCO), and the anterior scleral surface were manually segmented. PCT was measured at 100, 300, 500, 700, 900, and 1100 μm from the ASCO globally and within 12 clock-hour sectors. The effects of age, axial length, intraocular pressure, ethnicity, sex, sector, and ASCO area on PCT were assessed by ANOVA and univariable and multivariable regressions.

RESULTS. Globally, PCT was thicker further from the ASCO border and thinner with older age, longer axial length, larger ASCO area, European descent, and female sex. Among these effectors, age and axial length explained the greatest proportion of variance. The rate of age-related decline increased further from the ASCO border. Sectorally, the inferior-temporal sectors were thinnest (10.7%–20.0% thinner than the thickest sector) and demonstrated a higher rate of age-related loss (from 15.6% to 20.7% faster) at each ASCO distance.

CONCLUSIONS. In healthy eyes, PCT was thinnest in the inferior temporal sectors and thinner PCT was associated with older age, European descent, longer axial length, larger ASCO area, and female sex. Among these associations, age had the strongest influence, and its effect was greatest within the inferior temporal sectors.

Keywords: peripapillary choroid, glaucoma, optic nerve head, 3D imaging, optical coherence tomography, peripapillary atrophy, imaging anatomy

Optical coherence tomography (OCT) permits the visualization and segmentation of Bruch’s membrane, Bruch’s membrane opening (BMO), the anterior scleral surface, the neural canal boundary, and the anterior scleral canal opening (ASCO; Figs. 1, 2).1 Using these OCT landmarks to measure peripapillary choroidal thickness (PCT) enables both its cross-sectional characterization in healthy and diseased eyes and the longitudinal detection of PCT change in the locations that give rise to peripapillary atrophy (Fig. 3). The contribution of PCT and its change over time to the detection of glaucoma and other progressive conditions such as degenerative myopia can thus be assessed.

Alteration to the tissues of the peripapillary sclera, posterior ciliary arteries, choroid, and retina are thought to underlie the various clinical presentations of peripapillary atrophy in aging, glaucoma, and myopia.2–8 Hayreh9 and others10–11 have hypothesized that peripapillary atrophy in glaucoma is a manifestation of compromised peripapillary choroidal blood flow within the posterior ciliary artery branches that penetrat ed the sclera immediately adjacent to the ASCO (hereafter...
FIGURE 1. Manual segmentation of each radial B-scan. (A) A representative 15° radial B-scan is shown with its location depicted in green within the inlaid infrared reflectance (IR) image (bottom left). (B) Manually segmented ONH landmarks for this study within the B-scan shown in (A). Orange lines/points are the posterior surface of the Bruch’s Membrane/RPE complex, gold lines/points are the anterior surface of the sclera. Green lines/points are the neural canal wall, red points are BMO, and blue points are the ASCO. (C) Point cloud of segmented points from the complete set of 24 radial B-scans obtained for this ONH.
FIGURE 2. Measurement of peripapillary choroidal thickness at six distances (measured in microns) from the ASCO within the ASCO reference plane. Within the three-dimensional point cloud of segmented points from each OCT ONH data set (Figure 1C, above), Bruch’s membrane and anterior scleral surface points were interpolated using b-splines. PCT was assessed in microns at six distances (vertical blue dotted lines) from the ASCO, measured within the ASCO reference plane (horizontal blue line). Each measurement distance was projected from the ASCO to the anterior sclera surface (yellow dots). At each anterior scleral measurement point, PCT was defined by the minimum distance to the posterior surface of Bruch’s membrane (green arrows): PCT-100, PCT-300, PCT-500, PCT-700, PCT-900, and PCT-1100, respectively. In this study, PCT measurements within the regions of border tissues of Elschnig (BTE) obliqueness (pink externally oblique, left; blue internally oblique, right) were not included in the normative values as explained in Figure 3.

FIGURE 3. Although regions of internally and externally oblique BTE are defined by the offset of OCT BMO relative to OCT ASCO, PCT measurements within these regions are not included in the normative values of this report. (A) Color optic disc photo of the study eye of subject FDA287, with colocalized OCT ASCO (blue) and OCT BMO (red) points. The location and orientation (B1–B2) and (D1-D2) of the cropped B-scans shown in B, C and D, E are shown. (B) Cropped superior-nasal B-scan in a region of internally oblique BTE, (B1-B2) shown in A and delineated in (C). Note that BMO is “internal” to ASCO (or closer to the center of the disc). Note also that the suggestion of a juxta-scleral canal posterior ciliary vessel entering the choroid from the sclera (red dots). (D) Cropped inferior-temporal B-scan in a region of externally oblique BTE (D1-D2) shown in A and delineated in (E). Note that BMO is “external” to ASCO (or farther from the center of the disc). Although externally oblique border tissues do not represent atrophy in any form, they are commonly referred to as gamma peripapillary atrophy in the clinical55 and OCT4,56,57 literature. (F) The clinical extent of internally (blue) and externally (pink) oblique BTE in a healthy study eye with mild myopia (spherical equivalent –4.25D, axial length 25.15 mm). In this cross-sectional study, PCT measurements within the regions of BTE obliqueness were not included in the normative values because when present the density of the border tissues themselves and the adjacent choroidal septa made the presence of active choroidal vasculature difficult to determine and because the occurrence and regional distribution of internally and externally oblique border tissues are not consistent among all human eyes.20 However, PCT can be measured relative to the ASCO within both forms of oblique border tissue regions, and the individual eye longitudinal change within these regions may be clinically important.
referred to as the juxta-scleral canal posterior ciliary artery branches; Fig. 3). These branches are important because they also supply the circle of Zinn-Haller, the laminar beam capillaries, and the retrolaminar orbital optic nerve and may thus separately contribute to the optic nerve head (ONH) pathophysiology of aging, glaucoma, and myopia.

As a first step toward using OCT measurements of PCT in the detection of glaucoma or pathological myopia and their progression, the purpose of the present study was to measure PCT in a large group of healthy eyes relative to the ASCO at six proximal to distal measurement locations (100 μm, 300 μm, 500 μm, 700 μm, 900 μm, and 1100 μm, respectively). A second purpose of this study was to report and compare the influence of age, axial length, ethnicity, sex, IOP, and ASCO area on peripapillary choroidal thickness at each measurement location both globally and by foveal-BMO (FoBMO) 30° sectors.

The majority of studies in which PCT is measured by OCT employ BMO as the reference opening for its regional quantification and Bruch’s membrane as the reference for the thickness measurement. PCT is measured from Bruch’s membrane to the anterior scleral surface at measurement points that are located at fixed distances along Bruch’s membrane from BMO. In this study, PCT was assessed at six distances from the ASCO, measured within an ASCO reference plane. Each measurement location was projected to the anterior sclera surface from which a measurement to Bruch’s membrane was made (Fig. 2). We chose this approach for four reasons. First, BMO can be difficult to distinguish within the temporal region of myopic eyes. Second, segmenting both the ASCO and BMO in a given eye primarily identifies the location and extent of oblique border tissue regions (Fig. 3). Third, we believe that the ASCO and the anterior scleral surface will be more stable as anatomic landmarks than BMO and Bruch’s membrane during the course of peripapillary choroidal thinning in aging, glaucoma, and myopia. Fourth, measurement locations within an ASCO reference plane should be less influenced by disease-related distortions in the ASCO or anterior scleral canal surface.

In the present cross-sectional study, we do not include PCT measurements within oblique border tissue regions because the density of the border tissues themselves and the adjacent choroidal septa make the presence of active choroidal vasculature difficult to determine (Fig. 3) and because the regional distribution and extent of internally and externally oblique border tissues are not consistent among human eyes. However, we predict that oblique border tissue regions will be most susceptible to longitudinal PCT thinning because PCT is the thinnest in these regions (Fig. 3). We further predict that longitudinal thinning within the border tissue regions will precede the onset and progression of peripapillary microvascular dropout and atrophy in the aging, glaucomatous, and myopic eye. Our proposed method can enable longitudinal PCT measurements to be made in the internally and externally oblique border tissue regions of at-risk eyes, thereby allowing the clinical timing of longitudinal OCT PCT thinning and OCT angiographic change to be assessed.

**Methods**

**Conventions**

A detailed description of our study participants and our methods of data acquisition has been previously published. We use the term ONH to refer to the tissues that are contained within the scleral canal and those immediately adjacent to it (i.e., the peripapillary sclera, choroid, and retina as well as the retrolaminar optic nerve). PCT is the distance between the anterior scleral surface and Bruch’s membrane and is always a positive number or zero. Factors that have positive and negative effects on PCT correlate to thicker and thinner PCT, respectively. Global PCT refers to PCT without regard to sector.

**Participants**

A total of 362 healthy individuals participated in this study: 246 self-identified European descent; 47 Hispanic ethnicity, 47 African descent, 19 Asian descent, and 3 Native American descent participants. The participants were recruited to represent the ethnic composition of the U.S. population as mandated by the U.S. Food and Drug Administration. Consent documents approved by the institutional review board were signed by each participant. The study adhered to the Declaration of Helsinki for research involving human participants.

At the first visit, medical and ophthalmic histories were obtained, followed by anterior segment and external eye examinations, Van Herrick angle assessment, crystalline lens evaluation, standard Snellen or Early Treatment Diabetic Retinopathy Study visual acuity, refraction, central keratometry, and axial length assessments. Standard automated perimetry (Humphrey Field Analyzer [Carl Zeiss Meditec, Dublin, CA, USA], 24–2 Swedish Interactive Thresholding Algorithm), was repeated once if deemed unreliable or outside normal limits (see below). OCT examination, ophthalmoscopic examination of the posterior pole, and stereophotography were followed by Goldmann tonometry and pachymetry.

Inclusion criteria included age 18 to 90 years old; no history of glaucoma, IOP ≤ 21 mm Hg; best corrected visual acuity ≥ 20/40, refraction less than ±6.00 diopter (D) sphere and ±2.00 D cylinder; (4) Glaucoma Hemifield Test and mean deviation within normal limits. Exclusion criteria included unusable stereo photographs or insufficient OCT image quality (quality score < 20); clinically abnormal optic disc appearance; any intraocular surgery (except uncomplicated cataract surgery) or vitreous, retinal, choroidal, or neuroophthalmological disease; and ethnic group other than those listed. All test procedures were performed on both eyes of each participant, but only one eye was randomized for analysis.

**OCT Image Acquisition and Segmentation**

The ONH, peripapillary retinal nerve fiber layer (RNFL) and macula were imaged with spectral domain OCT (Spectralis, Heidelberg Engineering GmbH, Heidelberg, Germany; software version Heyex 1.9.10.0). For each eye, prior to image acquisition, refractive correction and keratometry values were entered into the instrument data base and the operator manually defined the fovea with a live B-scan, then centered the imaging field on the ONH, where the two BMO points in each of two perpendicular ONH radial B-scans were identified. These steps established the eye-specific, FoBMO axis that was used as the reference for the acquisition of all scans. The complete ONH imaging pattern consisted of 24 radially equidistant, 15° B-scans (768 A-lines each) centered on the BMO and acquired in enhanced depth imaging mode, with an average of 25 repetitions each.

Our strategy for OCT ONH image manual segmentation has been described previously (Fig. 1). Raw OCT volumes along with automatic segmented BMO points were exported from the device and imported into our custom three-dimensional visualization and segmentation software (ATL 3D Suite). ONH and peripapillary landmarks were manually segmented in each radial B-scan (24 total) of each OCT volume. Segmented landmarks included the internal limiting membrane, posterior surface of the RNFL, posterior surface of Bruch’s membrane/
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PCT was measured at six distances from the ASCO (hereafter referred to as ASCO measurement distances: 100 μm [PCT-100], 300 μm [PCT-300], 500 μm [PCT-500], 700 μm [PCT-700], 900 μm [PCT-900], and 1100 μm [PCT-1100]) measured within the ASCO reference plane and projected to the anterior scleral surface (Fig. 2). At each anterior scleral measurement point, PCT was defined by the minimum distance to the posterior surface of Bruch’s membrane. However, when internally or externally oblique border tissues were present in a given study eye (Fig. 5), PCT measurements within the regions of internally and externally oblique border tissues (most often at 100 μm and 300 μm measurement points) were not included in the normative values because the density of the border tissues themselves and the adjacent choroidal septa made the presence of active choroidal vasculature difficult to determine. Global and sectoral %PCT were calculated for each study eye, at each ASCO distance, as the PCT divided by the mean PCT of the study population at that location. ASCO area was calculated after projection of the ASCO points onto the ASCO reference plane, as previously reported.1

Regionalization

Twelve 30° sectors (centered on each clock hour) were established relative to the FoBMO axis as previously described (Fig. 4).1,26

Interobserver Reproducibility

Interobserver segmentation reproducibility was assessed at each PCT measurement distance by having four observers each segment the same eight OCT data sets. For each OCT data set, global and sectoral values for PCT at all six ASCO measurement distances were computed for each observer. Interobserver reproducibility for ASCO area has been previously reported.1

Statistical Analysis

All statistical analyses were performed in R version 3.1.3 (The R Foundation for Statistical Computing, Vienna, Austria). Intra-class correlation coefficients (ICC) between observers for each global and sectoral parameter (i.e., one global value and 12 sectoral value per distance per participant per observer) were calculated using a 2-way analysis of variance (ANOVA).29,30

The effects of measurement distance from the ASCO, age, axial length, sex, ethnicity, and IOP on overall global PCT were assessed within an ANOVA by general linear model using generalized estimation equation (GEEGLM). Univariate regression models were formed to relate global PCT at each measurement location with age, ASCO area, axial length, and IOP. The significance and magnitude of the effects of age, axial length, ASCO area, IOP, sex, and ethnicity on global PCT at each measurement location were assessed by calculating the proportion of the total variance ($R^2$) within an ANOVA with a linear regression model. Coefficients for each of these effects on global choroidal thickness at each measurement location were also assessed within a multivariate linear regression model.

For sectoral PCT, an initial overall ANOVA was performed with a generalized estimation equation model to assess the significance of age, ASCO area, axial length, sex, ethnicity, sector, ASCO distance, sector versus age, measurement distance versus age, measurement distance versus sector, and distance versus sector versus age. A follow-up ANOVA was then performed to assess the significance of age, ASCO area, axial length, sex, ethnicity, sector, and sector-versus-age effects on sectoral choroidal thickness at each measurement location.
Tables 1 and 2. Mean PCT was 108.81 ± 0.78 m at the PCT-1100 measurement point, increased to 172.47 ± 0.8 m at the PCT-100 measurement point. In the univariate regression models, age was negatively associated with PCT at all distances (P < 0.0001; R² values for each model ranging from 0.13–0.16; Fig. 5). The effect of age on PCT became more pronounced with increasing distance (>0.59 µm/year at PCT-100, progressively increasing to >1.43 µm/year at PCT-100; Fig. 5). Axial length was weakly negatively associated with PCT at all distances (P < 0.01; R² values for each model ranging from 0.02–0.06; Supplementary Fig. S1).
**FIGURE 5.** Scatterplot and univariate linear regression of PCT and age at each measurement point. Panels depict data at the 100, 300, and 500 μm measurement distances above and the 700, 900, and 1100 μm distances below. The slope of the regression line achieved significance at the $P < 0.0001$ level at all distances from the ASCO. Solid blue lines indicate fitted linear regression lines; dotted blue curves indicate the 95% CI of the regression lines; gray circles with black border indicate individual eye values.

**TABLE 3.** Multivariable Regression Coefficients for Demographic, Ocular, Sex, and Ethnicity Effects on PCT at Each Measurement Distance From the ASCO

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PCT-100</th>
<th>SE</th>
<th>PCT-300</th>
<th>SE</th>
<th>PCT-500</th>
<th>SE</th>
<th>PCT-700</th>
<th>SE</th>
<th>PCT-900</th>
<th>SE</th>
<th>PCT-1100</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>295.14</td>
<td>36.69</td>
<td>472.55</td>
<td>45.98</td>
<td>612.77</td>
<td>55.21</td>
<td>711.54</td>
<td>62.91</td>
<td>783.92</td>
<td>68.52</td>
<td>818.43</td>
<td>72.91</td>
</tr>
<tr>
<td>Age</td>
<td>-0.62</td>
<td>0.08</td>
<td>-0.87</td>
<td>0.10</td>
<td>-1.14</td>
<td>0.12</td>
<td>-1.35</td>
<td>0.14</td>
<td>-1.51</td>
<td>0.15</td>
<td>-1.63</td>
<td>0.16</td>
</tr>
<tr>
<td>ASCO area</td>
<td>-6.10</td>
<td>3.19</td>
<td>-11.4</td>
<td>3.96</td>
<td>-15.27</td>
<td>4.80</td>
<td>-16.95</td>
<td>5.47</td>
<td>-17.6</td>
<td>5.96</td>
<td>-22.43</td>
<td>6.83</td>
</tr>
<tr>
<td>IOP</td>
<td>-0.21</td>
<td>0.48</td>
<td>-0.33</td>
<td>0.62</td>
<td>-0.73</td>
<td>0.75</td>
<td>-0.92</td>
<td>0.85</td>
<td>-1.04</td>
<td>0.93</td>
<td>-1.04</td>
<td>1.00</td>
</tr>
<tr>
<td>Sex (male vs. female)*</td>
<td>4.83</td>
<td>2.72</td>
<td>6.16</td>
<td>3.45</td>
<td>8.86</td>
<td>4.15</td>
<td>11.07</td>
<td>4.73</td>
<td>12.4</td>
<td>5.15</td>
<td>12.54</td>
<td>5.53</td>
</tr>
<tr>
<td>Ethnicity and race</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic ethnicity‡ vs. European descent†</td>
<td>10.65</td>
<td>4.06</td>
<td>19.35</td>
<td>5.19</td>
<td>25.30</td>
<td>6.22</td>
<td>30.04</td>
<td>7.09</td>
<td>32.67</td>
<td>7.72</td>
<td>34.75</td>
<td>8.42</td>
</tr>
<tr>
<td>African descent‡ vs. European descent†</td>
<td>9.90</td>
<td>4.02</td>
<td>27.64</td>
<td>5.13</td>
<td>36.33</td>
<td>6.22</td>
<td>41.57</td>
<td>7.09</td>
<td>43.15</td>
<td>7.72</td>
<td>43.79</td>
<td>8.17</td>
</tr>
<tr>
<td>Asian and Native American descent vs. European descent‡</td>
<td>-4.56</td>
<td>6.21</td>
<td>-3.59</td>
<td>7.22</td>
<td>-4.42</td>
<td>8.57</td>
<td>-6.81</td>
<td>9.77</td>
<td>-9.27</td>
<td>10.64</td>
<td>-9.95</td>
<td>11.25</td>
</tr>
</tbody>
</table>

**Bold indicates** $P \leq 0.05$.

* Parameter in the male participants was compared to the same parameter in the reference female participants.

† Parameters in African descent, Hispanic ethnicity, and Asian and Native American descent participants were compared with the same parameters in reference European descent participants separately.

‡ African descent and Hispanic ethnicity participants were not significantly different overall or at any measurement distance.
In multivariable analysis, increased age and axial length were negatively associated with PCT at all measurement distances (Table 3, model $R^2 = 0.23–0.34$). Increased ASCO area was also negatively associated with PCT for all distances $\geq 300 \mu m$ from the ASCO. PCT was thicker in eyes of African descent and Hispanic ethnicity at all measurement distances than European descent eyes (PCT-100: African 118.27 ± 20.91 $\mu m$, Hispanic 118.74 ± 23.13 $\mu m$, European 105.76 ± 26.65 $\mu m$; PCT-1100: African 208.39 ± 56.35 $\mu m$, Hispanic 200.62 ± 61.45 $\mu m$, European 162.58 ± 60.53 $\mu m$; $P < 0.01$; Fig. 6).

Differences between the African descent and Hispanic ethnicity groups did not achieve statistical significance at any distances ($P = 0.173$ to 0.887). The effectors that contributed most to explaining the variability of global PCT at each measurement distance were age (ranging from 13%–16%), axial length (ranging from 4%–10%), ethnicity (ranging from 2%–6%), ASCO area (ranging from 1%–2%), and sex (1%), respectively.

**Sectoral PCT**

PCT was thinnest within the inferior–nasal, inferior, inferior–temporal, and temporal sectors at all measurement distances (Fig. 7, upper row). The sectors with the thinnest PCT were significantly different from the sectors with the thickest PCT at all measurement distances (Fig. 7, upper row; $P \leq 0.05$, general linear regression by GEEGLM).

The effect of sector on PCT remained significant after adjusting for all other effectors at each measurement distance (ANOVA; Supplementary Table S1). Sectoral PCT was significantly influenced by age, ASCO area, axial length, ethnicity, sex, sector, measurement distance from the ASCO, and the interactions between sector versus age, measurement distance versus age, measurement distance versus sector, and measurement distance versus sector versus age, by ANOVA (by GEEGLM, $P \leq 0.05$). In a separate ANOVA (Supplementary Table S2), the effect of age and the effect of the sector-versus-age interaction on the %PCT were also significant at all measurement distances.

The thinnest sectors (upper row of Fig. 7) also demonstrated the most rapid thinning with age (middle and lower panels, Fig. 7). At all six measurement distances, the effects of age on PCT and %PCT in the sectors with the fastest rate of age-related thinning were significantly greater ($P \leq 0.05$, general linear regression by GEEGLM model) than the effects of age in the sectors with the slowest rates of age-related thinning (Fig. 7, middle and lower rows). Age-related PCT reduction was from 15.6% to 20.7% greater in the faster sectors when compared with the slower sectors at six measurement distances.

Although the sectoral distribution of PCT was similar at all measurement distances (thinnest inferiorly and inferior–temporally; Fig. 7, upper row), sectoral thickness variation increased substantially as the measurement distance from the ASCO increased. Sectoral PCT ranged from 101 to 115 $\mu m$ at the PCT-100 $\mu m$ measurement location and ranged from 143 to 189 $\mu m$ at the PCT-1100 $\mu m$ measurement location. Age-affected sectoral PCT (Fig. 7, middle row) and %PCT (Fig. 7, lower row) also increased in magnitude and variation as the distance from ASCO increased. Sectoral age effects on %PCT ranged from $-0.52 \text{ to } -0.69 \%/y$ at the PCT-100 $\mu m$ measurement location and from $-0.86 \text{ to } -1.18 \%/y$ at the PCT-1100 $\mu m$ measurement location.
DISCUSSION

This study characterizes PCT in a large healthy population and introduces both the use of the ASCO as the neural canal reference opening for its measurement and the use of the FoBM0 axis as the common horizontal axis for its regionalization. Our findings suggest that OCT PCT is thinnest in the inferior temporal sectors and thinnest closest to the ASCO. Thinner PCT was associated with age, axial length, European descent, and weakly associated with larger ASCO area and sex (middle row). The sectors with the top three slowest rates of change are bold black. The sectors with the top three fastest rates of change are bold blue. The rates of change of the fastest sectors are significantly faster than the slowest sectors when they are accompanied by a number sign symbol (see below). The rate of PCT change with age in each sector (μm/y), after adjusting for axial length, ASCO area, IOP, ethnicity, and sex (middle row). The sectors with the top three slowest rates of change are bold black. The sectors with the top three fastest rates of change are bold blue. The rates of change of the fastest sectors are significantly faster than the slowest sectors when they are accompanied by a number sign symbol (legend below). The rate of %PCT change with age in each sector after adjusting for the same covariates (lower row). The sectors with the three lowest rates of %PCT change are bold black. The sectors with the three fastest rates of %PCT change are shown in bold blue. Significant differences, by a general estimation equation model are depicted by ***P < 0.001; **P < 0.01; and *P < 0.05, respectively.

The peripapillary choroid was thinnest within the inferior sectors of our study eyes, which agrees with a series of previous reports.15,17,52,54,41,43,44 However, our finding that...
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