Relationship Between Peripapillary Choroid and Retinal Nerve Fiber Layer Thickness in a Population-Based Sample of Nonglaucomatous Eyes

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• PURPOSE: To describe the relationship between peripapillary choroidal thickness and retinal nerve fiber layer (RNFL) thickness in a population-based sample of nonglaucomatous eyes.

• DESIGN: Population-based, cross-sectional study.

• METHODS: A total of 478 nonglaucomatous subjects aged over 40 years were recruited from the Singapore Malay Eye Study (SiMES-2). All participants underwent a detailed ophthalmic examination, including Cirrus and Spectralis optical coherence tomography (OCT) for the measurements of RNFL thickness and peripapillary choroidal thickness, respectively. Associations between peripapillary choroidal thickness and RNFL thickness were assessed using linear regression models with generalized estimating equations.

• RESULTS: Of the 424 included subjects (843 nonglaucomatous eyes), 60.9% were women, and the mean (SD) age was 66.74 (10.44) years. The mean peripapillary choroidal thickness was 135.59 ± 56.74 μm and the mean RNFL thickness was 92.92 ± 11.41 μm. In terms of distribution profile, peripapillary choroid was thickest (150.04 ± 59.72 μm) at the superior and thinnest (110.71 ± 51.61 μm) at the inferior quadrant, whereas RNFL was thickest (118.60 ± 19.83 μm) at the inferior and thinnest (67.36 ± 11.36 μm) at the temporal quadrant. We found that thinner peripapillary choroidal thickness (PPCT) was independently associated with thinner RNFL thickness globally (regression coefficient [β] = −1.334 μm for per-SD decrease in PPCT, $P = .003$), and in the inferior (β = −2.565, $P = .001$) and superior (β = −2.340, $P = .001$) quadrants even after adjusting for potential confounders.

• CONCLUSIONS: Thinner peripapillary choroid was independently associated with thinner RNFL globally and in the inferior and superior regions. This structure-structure relationship may need further exploration in glaucomatous eyes prior to its application in clinical settings. (Am J Ophthalmol 2016;161:4–11. © 2016 by Elsevier Inc. All rights reserved.)

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RETINAL NERVE FIBER LAYER (RNFL) THICKNESS changes are the earliest signs of glaucoma. These precede even optic nerve head (ONH) and visual field changes,[1,2] making the evaluation of RNFL thickness a crucial assessment in the early diagnosis of glaucoma.[3–5] Among the various factors associated with the development and progression of glaucoma, vascular and hemodynamic factors have been suggested to play an important role.[6,7] Studies[8,9] have now demonstrated vascular insufficiency of the ONH to be an important parameter in the pathogenesis of glaucomatous optic neuropathy. Since RNFL is formed by the expansion of the fibers of the optic nerve, any insufficient blood supply to the ONH could lead to thinner RNFL causing glaucomatous optic neuropathy.

Because of the common source of blood supply to the ONH and peripapillary choroid via the short posterior ciliary arteries,[10–13] it is likely that a relationship exists between peripapillary choroid and RNFL thickness. However, to date, no studies have explored the quantitative relationship between these parameters in normal subjects, particularly in the general population. Evaluation of the association between peripapillary choroidal thickness and RNFL thickness may help better elucidate the relationship between the structural parameters that may be useful clinically for assessment of ONH damage in glaucoma.

With the recent advancement in imaging technology using spectral-domain optical coherence tomography (SD OCT), in particular the enhanced depth imaging (EDI)

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technique of SD OCT, objective and quantitative assessment of the peripapillary choroidal thickness is now possible. The purpose of this population-based, cross-sectional study was to evaluate the relationship between peripapillary choroidal thickness and RNFL thickness as measured by SD OCT in a large population sample of nonglaucomatous subjects. We further report the distribution profile of peripapillary choroidal thickness obtained using our automated choroidal segmentation software[14] and RNFL thickness in our population.

METHODS

• **STUDY POPULATION AND DESIGN:** Subjects of this study were enrolled from the Singapore Malay Eye Study (SiMES), a population-based cohort study of eye diseases in a Malay population aged 40–80 years in Singapore. The baseline examination was conducted between 2004 and 2006 and a follow-up examination of the SiMES participants was conducted between January 2011 and December 2013.[15] For this study, we consecutively recruited 478 subjects from SiMES participants who attended the follow-up examination from February 2012 to July 2013. Written informed consent was obtained from all participants after explanation of the nature and possible consequences of the study. The study adhered to the tenets of the Declaration of Helsinki, and ethics approval was obtained from the Singapore Eye Research Institute Institutional Review Board.

• **OCULAR EXAMINATIONS:** Each study participant underwent a standard ophthalmic examination including measurement of refraction and visual acuity, slit-lamp biomicroscopy, tonometry, pachymetry, perimetry, ocular biometry, fundus examination, and SD OCT imaging. Refraction and corneal curvature were measured using an autokeratorefractometer (Canon RK 5 Auto Ref-Keratometer; Canon Inc Ltd, Tochigiken, Japan). Spherical equivalent (SE) was calculated as the sum of the spherical power and half of the cylinder power. Best-corrected visual acuity (BCVA) was measured monocularly using a logarithm of the minimal angle of resolution (logMAR) chart (Lighthouse International, New York, New York, USA) at a distance of 4 m. Central corneal thickness was measured using an ultrasound pachymeter (Advent; Mentor O & O Inc, Norwell, Massachusetts, USA). Ocular biometry, including axial length (AL), was measured using noncontact partial coherence interferometry (IOL Master V3.01; Carl Zeiss Meditec AG, Jena, Germany). Intraocular pressure (IOP) was measured using Goldmann applanation tonometry (Haag-Streit, Bern, Switzerland) before pupil dilation. Standardized visual field testing was performed with static automated white-on-white threshold perimetry (SITA Fast 24-2, Humphrey Field Analyzer II; Carl Zeiss Meditec, Inc, Oberkochen, Germany). Slit-lamp biomicroscopy (Haag-Streit model BQ-900; Haag-Streit) was performed by the study ophthalmologists to examine the anterior chamber and lens after pupil dilation with tropicamide 1% and phenylephrine hydrochloride 2.5%.

Glaucoma was defined using the International Society of Geographic and Epidemiological Ophthalmology scheme,[16] based on findings from gonioscopy, optic disc characteristics, and visual fields results (as described below).

• **VISUAL FIELD EXAMINATION:** Standardized visual field testing was performed with static automated perimetry (Swedish Interactive Threshold Algorithm standard 24-2, Humphery Field Analyzer II; Carl Zeiss Meditec, Dublin, California, USA). A visual field was defined as reliable when fixation losses were less than 20%, and false-positive and false-negative rates were less than 33%. A glaucomatous visual field defect was defined as the presence of 3 or more significant ($P < .05$) nonedge continuous points with at least 1 at the $P < .01$ level on the same side of the horizontal meridian in the pattern deviation plot, and classified as "outside normal limits" on the Glaucoma Hemifield Test, confirmed on 2 consecutive visual field examinations.

SiMES is part of the Singapore Epidemiology Eye Diseases (SEED) study.[17] For the purpose of conformity between other studies in SEED, we have used Cirrus HD-OCT for RNFL thickness measurements and Spectralis SD OCT with EDI for choroidal measurements. In addition, we believe that the use of 2 SD OCT machines has its own advantages, as systematic measurement error in 1 machine, if existing, could lead to a biased association between peripapillary choroidal thickness and RNFL thickness, whereas this could be taken care of by the use of 2 machines.

• **RETINAL NERVE FIBER LAYER IMAGING AND MEASUREMENT:** Cirrus HD-OCT (software version 6.0; Carl Zeiss Meditec, Inc, Dublin, California, USA) was used to measure peripapillary RNFL. After pupil dilation, RNFL scan acquisitions were performed for each participant using an optic disc cube 200 × 200 scan protocol, which generates a cube of data in a 6 mm × 6 mm grid with 200 × 200 axial measurements. In brief, the subject's pupil was first centered and focused in an iris viewing camera on the acquire screen, and the line scanning ophthalmoscope (LSO) with "auto focus" mode was then used to optimize the view of the retina. The "center" and "enhance" modes were used to optimize the Z-offset and scan polarization, respectively, for the OCT scan to maximize the OCT signal. Rescanning was performed if a motion artifact or saccades through the calculation circle (3.46 mm diameter around the ONH) were detected. The OCT scans were excluded if there was the presence of RNFL or ONH