

Reproducibility of Neuroretinal Rim Measurements Obtained from High-Density Spectral Domain Optical Coherence Tomography Volume Scans

Janice Kim^{1,3}, Clara J Men^{2,4}, Kitiya Ratanawongphaibul^{1,2,5}, Georgia Papadogeorgou⁶, Edem Tsikata^{1,2}, Geulah S Ben-David^{1,2,7}, Hussein Antar^{1,8}, Linda Yi-Chieh Poon^{1,9}, Madeline Freeman^{1,10}, Elli A Park^{1,11}, Maria A Guzman Aparicio^{1,2}, Johannes F de Boer^{12,13}, Teresa C Chen^{1,2}

¹Department of Ophthalmology, Glaucoma Service, Massachusetts Eye and Ear Infirmary, Boston, MA, USA; ²Harvard Medical School, Boston, MA, USA; ³Department of Ophthalmology, Edward S. Harkness Eye Institute, Columbia University Irving Medical Center, New York, NY, USA; ⁴Shiley Eye Institute at University of California, San Diego, CA, USA; ⁵Center of Excellence in Glaucoma, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand; ⁶Department of Statistics, University of Florida, Gainesville, FL, USA; ⁷Department of Ophthalmology, Emek Medical Center, Afula, Israel; ⁸University of Massachusetts Medical School, Worcester, MA, USA; ⁹Department of Ophthalmology, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan; ¹⁰Smith College School for Social Work, Northampton, MA, USA; ¹¹Boston University School of Medicine, Boston, MA, USA; ¹²LaserLab Amsterdam, Department of Physics and Astronomy, Vrije Universiteit, Amsterdam, The Netherlands; ¹³Department of Ophthalmology, Amsterdam University Medical Centers, Amsterdam, The Netherlands

Correspondence: Teresa C Chen, Department of Ophthalmology, Glaucoma Service, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA, 02114, USA, Tel +1 (617) 573-3674, Fax +1 (617) 573-3707, Email teresa_chen@meei.harvard.edu

Purpose: To compare the reproducibility of two-dimensional (2D) peripapillary retinal nerve fiber layer (RNFL) thickness and three-dimensional (3D) neuroretinal rim measurements using spectral domain optical coherence tomography (SDOCT) in normal and glaucoma subjects.

Methods: One eye per subject for 27 normal and 40 glaucoma subjects underwent repeat SDOCT RNFL thickness scans and optic nerve volume scans on the same day. From the volume scan, custom software calculated five neuroretinal rim parameters: 3D minimum distance band (MDB) thickness, 3D MDB area, 3D rim volume, 2D rim area, and 2D rim thickness. Within-subject variance (Sw), coefficient of variation (CV), and intraclass correlation coefficient (ICC) were analyzed.

Results: MDB thickness and RNFL thickness have similar reproducibility among normal and glaucoma subjects (eg, global MDB thickness CVs of 2.4% and 3.6%, and global RNFL thickness CVs of 1.3% and 2.2%; $P > 0.05$ for both comparisons). Reproducibility of MDB thickness was lower in glaucoma patients for the superior and inferior quadrants compared to normal subjects (CVs of 9.6% versus 3.4% and 6.9% versus 2.7%; $P < 0.05$, respectively). There were no statistically significant differences between both groups for RNFL thickness in the four quadrants. For both patient groups and for all regions, MDB thickness had the lowest CVs among all five neuroretinal rim parameters (eg, global MDB thickness CVs of 2.4% and 3.6% versus 3.0% and 18.9% for the other four neuroretinal rim parameters).

Conclusion: Global MDB and global RNFL thickness are similarly reproducible among normal and glaucoma subjects, though MDB thickness for the superior and inferior quadrants is less reproducible among glaucoma subjects.

Keywords: glaucoma, optical coherence tomography, reproducibility, optic nerve, minimum distance band

Plain Language Summary

The minimum distance band (MDB) neuroretinal rim thickness parameter is a new high-density three-dimensional (3D) optical coherence tomography (OCT) measurement, which is reproducible and can help diagnose and monitor glaucoma.

Introduction

Early detection is the key to vision preservation. Once glaucoma progression is detected, treatment can be escalated, in order to prevent irreversible glaucomatous vision loss. A cardinal feature of spectral domain optical coherence

tomography (SDOCT) progression is change or loss greater than expected test–retest variability. Therefore, knowledge of normal test–retest variability, which is greater than normal age-related loss, is essential to know for any practicing ophthalmologist. Many ophthalmologists are aware of the “rule of 5s”, where any change of 5 μm or more is greater than expected normal test–retest variability for global retinal nerve fiber layer (RNFL) thickness^{1,2}; however, what is the normal expected test–retest variability for neuroretinal rim thickness in three-dimensional (3D) space? This paper answers that question.

This paper complements a recent study demonstrating that a novel high-density 3D minimum distance band (MDB) neuroretinal rim thickness parameter, which is a high-density version of the low-density commercially available Bruch’s membrane opening–minimum rim width (BMO–MRW), can detect glaucoma disease progression 1 to 2 years earlier than our best tests of structure (ie, disc photos and RNFL thickness measurements).³ Both the MDB and BMO–MRW quantify neuroretinal rim tissue in 3D space, and both have the cup surface as the inner border and the disc border as the outer surface. Both have also demonstrated equal or better diagnostic performance than the most commonly used two-dimensional (2D) RNFL thickness parameter (global RNFL thickness AUROCs [area under the receiver operating characteristics] 0.850 to 0.954 versus global MDB thickness AUROCs 0.884 to 0.969 and global BMO–MRW AUROCs 0.811 to 0.928).^{4–7} When comparing MDB with the BMO–MRW, there are two key differences: 1) the MDB parameter uses a high-density optic nerve volume scan (193 B-scans arranged in raster pattern), while the commercially available BMO–MRW uses a low-density optic nerve volume scan (24 B-scans arranged in radial pattern),^{6,7} and 2) the MDB disc border is defined as the retinal pigment epithelium/Bruch’s membrane complex (RPE/BM), while the BMO–MRW disc border is defined as BMO. Compared to the BMO–MRW with its BMO border, the MDB is easier to segment on SDOCT because the RPE/BM border is more consistently visible than BMO alone.⁸ Nevertheless, for the BMO–MRW neuroretinal rim parameter, previous studies have demonstrated excellent reproducibility in normal and glaucoma patients with coefficient of variations (CV) of 0.87–3.07%.^{5,9} However, the reproducibility for MDB neuroretinal thickness has not yet been as extensively studied as the reproducibility for BMO–MRW and current 2D glaucoma parameters, with the exception of a pilot study by Tsikata et al⁷ demonstrating that the mean inter-test variability for MDB thickness from 50 healthy and glaucoma subjects was 0.84% with a standard deviation of 5.18%.⁷ A simple software upgrade is all that is needed for SDOCT companies to incorporate this high-density MDB parameter into existing machines.

For SDOCT testing in glaucoma, the three cardinal structures to image are the peripapillary RNFL, the macula, and the optic nerve.^{5,10,11} For normal and glaucoma patients, current 2D glaucoma parameters of these three regions have shown similar reproducibility with global CVs ranging from 0.5% to 4.23%.^{10–16} However, clinical glaucoma practice is currently experiencing a paradigm shift from 2D to 3D imaging, and it is critical to know the inherent reproducibility of 3D parameters before making clinical decisions based on these newer parameters.

Using SDOCT in a cohort of normal and glaucoma patients, this study is unique in its aim to comprehensively evaluate not only the reproducibility of RNFL thickness but also five neuroretinal rim parameters [ie, two reference-plane independent (MDB thickness and area) and three reference-plane dependent (rim volume, rim area, rim thickness)]. We hypothesize that 3D glaucoma parameters, such as MDB neuroretinal rim thickness, will have good reproducibility for normal and glaucoma patients because they quantify optic nerve tissue in 3D space instead of along a 2D flat reference plane.

Methods

Study Participants and Examinations

The study protocol was approved by the Institutional Review Board of the Massachusetts Eye and Ear (MEE). All patients signed informed consents prior to enrolling in the study. All methods adhered to the tenets of the Declaration of Helsinki and were conducted in accordance with the Health Insurance Portability and Accountability Act. Study subjects were recruited from the Glaucoma Service at MEE between February 2012 and December 2016, as a part of the larger prospective SDOCT in Glaucoma (SIG) study of 2000 normal, glaucoma suspect, and glaucoma patients. All patients were examined by a glaucoma specialist (T.C.C.). Each patient underwent a complete ophthalmologic examination, including history, visual acuity testing, refraction, Goldmann applanation tonometry, slit-lamp

biomicroscopy, gonioscopy, ultrasound pachymetry, dilated ophthalmoscopy of the posterior segment, color disc photography (Visucam Pro NM; Carl Zeiss Meditec, Dublin, California), visual field (VF) testing (Swedish Interactive Threshold Algorithm 24–2 test of the Humphrey VF analyzer 750i; Carl Zeiss Meditec, Dublin, California), and optical coherence tomography (OCT) scans (Spectralis HRA+OCT, Heidelberg Engineering GmbH, Heidelberg, Germany).

To be eligible for this study, all participants met the following inclusion criteria: 1) a spherical equivalent between -5.0 diopters and $+5.0$ diopters; 2) reliable VF test results with $\leq 33\%$ fixation losses, $\leq 20\%$ false-positive results, and $\leq 20\%$ false-negative results; and 3) OCT scans with signal strength ≥ 15 . Subjects were excluded if they had any congenital anomalies of the anterior chamber, corneal scarring or opacities, severe non-proliferative or proliferative diabetic retinopathy, VF loss attributable to a non-glaucoma condition, or a dilated pupil diameter < 2 mm.

Healthy subjects were defined as having no ocular diseases, except for mild cataracts,¹⁷ and a normal glaucoma hemifield VF test result without visual field defects.¹⁸ Healthy subjects must also have had a best corrected visual acuity of 20/40 or better, intraocular pressures (IOP) < 21 mmHg, and inter-eye cup-to-disc asymmetry < 0.2 . Patients with physiologic cupping were included in this study as normal subjects as long as they met the above criteria.

Glaucoma patients with a best corrected visual acuity of 20/70 or better were included in the study. Glaucoma patients were identified as those with characteristic changes of the optic nerve with corresponding abnormal VF defects. The VF was considered abnormal if three or more contiguous test locations in the pattern deviation plot were depressed significantly at the $P < 5\%$ level with at least one at the $P < 1\%$ on the same side of the horizontal meridian or was classified as outside normal limits by the glaucoma hemifield test.¹⁹ Test locations on the outer rim were excluded from consideration to avoid rim artifacts. If both eyes of a participant were eligible for this study, one eye was selected using a random number generator.

Image Acquisition and Analysis of SDOCT High-Density Volumetric Scans

After pupillary dilation, each patient eye was imaged with the Spectralis OCT instrument using two scan protocols: a peripapillary RNFL circle scan and a $20^\circ \times 20^\circ$ volumetric scan centered on the optic nerve. The RNFL scan and the $20^\circ \times 20^\circ$ volumetric scan were performed twice for each eye on the same day, and each iteration was obtained at exactly the same location with the follow-up function. The RNFL scan was used to determine signal strength and scan quality in each patient. The volumetric protocol consisted of 193 horizontal raster scans, each with three frames averaged at the scan position.

Values for six diagnostic parameters (RNFL thickness, MDB thickness, MDB area, rim thickness, rim area, and rim volume) were calculated for the overall globe (360°), 90° quadrants (inferior, superior, nasal, and temporal), and 45° sectors [inferior-nasal (IN), superior-nasal (SN), inferior-temporal (IT), and superior-temporal (ST)]. RNFL thickness was calculated using Spectralis software (version 5.4.8.0). The five neuroretinal rim parameters (MDB thickness, MDB area, rim thickness, rim area, and rim volume) were calculated with C++ software built using the open-source libraries Insight Segmentation and Registration Toolkit (ITK version 4.3, Insight Software Consortium; Kitware, Clifton Park, New York). The program automatically segmented the internal limiting membrane (ILM) and RPE/BM complex in each raster scan to construct a 3D model (Figure 1A). The MDB thickness was calculated by measuring the shortest distances between 100 points spaced 3.6° apart on the optic disc margin (the termination of the RPE/BM complex) and the ILM (cup surface). The MDB area was measured by summing quadrilateral areas formed from two points on the disc margin and two points on the ILM. To calculate the other three rim parameters, a reference surface $150 \mu\text{m}$ above the RPE was used. The rim volume borders were defined by the ILM above, the $150 \mu\text{m}$ reference surface below, and the optic disc border radially (Figure 1B). Rim area was determined by measuring the projection of the rim tissue on the transverse plane (Figure 1C). Rim thickness was calculated as rim volume divided by rim area.

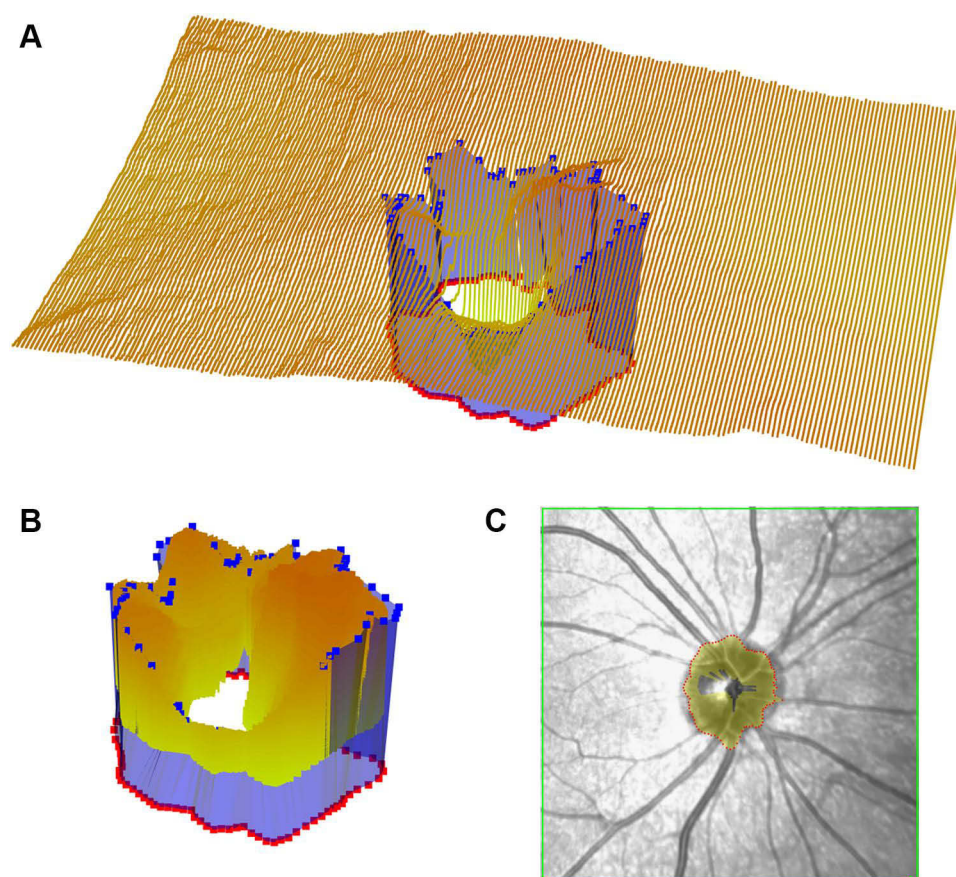


Figure 1 Minimum distance band, rim volume, and rim area. **(A)** The minimum distance band (blue) captures the shortest distance between the retinal pigment epithelium/Bruch's membrane opening, or disc border (red dots) and the internal limiting membrane, or cup surface (yellow lines). **(B)** The rim volume (solid yellow) is enclosed by the cup surface above, the 150 µm reference plane below (an invisible plane which lies 150 µm above and parallel to the disc border shown here in red), and laterally by the disc circumference. **(C)** The rim area (yellow) is the projection of the rim volume onto a flat surface.

Statistical Analysis

Statistical analyses were performed using R Statistical Software version 3.2.3. Demographics and ocular characteristics of the normal and glaucoma groups were compared using χ^2 tests for categorical variables and nonpaired two-tailed Student *t*-tests for continuous variables. The reproducibility for each diagnostic parameter was assessed by calculating the within-subject variance (Sw), CV, and intraclass correlation coefficient (ICC). The Sw represents the common standard deviation of repeated measurements. The Sw was calculated by averaging the variances or the squares of the standard deviations for all subjects and then taking the square root of the mean within-subject variance. The CV is the ratio of the standard deviation over the mean, where the standard deviation corresponds to the residual standard error from a regression model adjusting for patient and an indicator for each measurement. A one-way ANOVA was used to determine the ICC.²⁰ The one-way ANOVA included random effect for each subject in the study. Results with *P* values <0.05 were considered statistically significant. Intra-session test–retest variability was calculated as the Sw times 1.645 times the square root of 2. To estimate intra-session test–retest variability, true parameter measurement change in the level of deterioration required a one-tailed statistical test to estimate variance with 95% confidence.²¹

Results

A total of 78 participants with and without glaucoma met inclusion criteria and were enrolled. Of these 78 patients, 11 participants (14.1%) were excluded for the following reasons: poor image quality (5 participants, 45.5%), improper segmentation of volumetric scans (5 participants, 45.5%), and incomplete imaging (1 participant, 9.1%).

This left a total of 67 eligible participants for the study (27 normal participants and 40 glaucoma patients). Of the 40 glaucoma patients, 16 (40%) had mild glaucoma (mean deviation, MD ≥ -6 dB), 16 (40%) had moderate glaucoma (-12 dB \leq MD < -6 dB),

and 8 (20%) had severe glaucoma ($MD < -12$ dB), based on Hodapp–Parrish–Anderson criteria.²² The glaucoma population consisted of the following diagnoses: primary open angle (18 participants, 45.0%), normal tension (15 participants, 37.5%), pseudoexfoliation (4 participants, 10.0%), and pigmentary glaucoma (3 participants, 7.5%). Table 1 depicts the demographic and clinical characteristics of the patient sample population. Between the normal and glaucoma patients, there were no significant differences in the number of right eyes, gender, race, or spherical equivalent (Table 1). Glaucoma patients were significantly older than normal participants by 13.3 years ($P < 0.0005$ [Table 1]) and had a more negative MD and higher pattern standard deviation on visual field testing compared to the normal group ($P < 0.0005$ [Table 1]).

Tables 2 through 4 show mean parameter measurements (RNFL thickness, MDB thickness, MDB area, rim area, rim volume, rim thickness) for the various regions (global, quadrants, and sectors) for normal and glaucoma patients. For MDB thickness, MDB area, and rim area, glaucoma patients had significantly thinner mean measurements than normal participants for all regions (P value range: <0.0005 – 0.024 [Tables 3 and 4]). Among glaucoma patients, all regions,

Table 1 Patient Demographics

Parameter	Normal Participants	Glaucoma Patients	P*
Participants (N, % total)	27 (40.3%)	40 (59.7%)	
Right eyes (% total)	51.9	42.5	0.467
Age in years [mean + SD (range)]	55.8 ± 15.1 (22–82)	69.1 ± 9.4 (45–87)	<0.0005*
Female (% total)	59.2	57.5	1.000
Race (white; % total)	66.7	65.0	1.000
Spherical equivalent in diopters (mean + SD)	−0.31 ± 2.04	−0.64 ± 2.11	0.531
VF mean deviation in dB (mean + SD)	−0.51 ± 1.17	−7.59 ± 5.69	<0.0005*
VF pattern standard deviation in dB (mean + SD)	1.54 ± 0.29	6.76 ± 4.16	<0.0005*

Note: *Significantly different ($P < 0.05$) values.

Abbreviations: SD, standard deviation; VF, visual field.

Table 2 Spectralis Optical Coherence Tomography Retinal Nerve Fiber Layer (RNFL) Thickness Measurements (μ m) in Normal versus Glaucomatous Eyes

Region of Interest	Normal Patients (n=27) (Mean in μ m ± SD)	Glaucoma Patients (n=40) (Mean in μ m ± SD)	P*
Overall global	93.9 ± 13.9	69.0 ± 16.3	<0.0005*
Superior quadrant	115.4 ± 19.4	81.6 ± 24.2	<0.0005*
Temporal quadrant	69.4 ± 15.4	60.7 ± 15.8	0.092
Inferior quadrant	119.9 ± 24.4	78.5 ± 23.9	<0.0005*
Nasal quadrant	70.8 ± 14.9	55.1 ± 18.5	0.008*
ST sector	129.5 ± 19.2	89.8 ± 27.3	<0.0005*
IT sector	133.8 ± 24.4	84.3 ± 32.4	<0.0005*
SN sector	101.3 ± 22.8	73.4 ± 26.1	0.001*
IN sector	106.1 ± 31.2	72.7 ± 22.8	<0.0005*

Note: *Significantly different ($P < 0.05$) values.

Abbreviations: RNFL, retinal nerve fiber layer; SD, standard deviation; ST, superior-temporal; IT, inferior-temporal; SN, superior-nasal; IN, inferior-nasal.

Table 3 Spectralis Optical Coherence Tomography Neuroretinal Rim Measurements in Normal versus Glaucomatous Eyes

Reference-plane Independent Neuroretinal Rim Parameters			
MDB Thickness			
Region of Interest	Normal Patients (n=27) (Mean in $\mu\text{m} \pm \text{SD}$)	Glaucoma Patients (n=40) (Mean in $\mu\text{m} \pm \text{SD}$)	P*
Overall global	294.6 \pm 50.3	207.5 \pm 56.7	<0.0005*
Superior quadrant	326.4 \pm 59.5	226.5 \pm 72.4	<0.0005*
Temporal quadrant	224.9 \pm 49.7	180.8 \pm 51.4	0.008*
Inferior quadrant	334.1 \pm 63.3	209.7 \pm 65.1	<0.0005*
Nasal quadrant	294.7 \pm 52.9	213.3 \pm 70.3	<0.0005*
ST sector	322.2 \pm 62.4	221.0 \pm 78.7	<0.0005*
IT sector	314.9 \pm 66.2	188.9 \pm 73.2	<0.0005*
SN sector	332.7 \pm 61.4	233.8 \pm 70.6	<0.0005*
IN sector	353.4 \pm 65.0	230.7 \pm 68.1	<0.0005*
MDB Area			
Region of Interest	Normal Patients (n=27) (Mean in $\text{mm}^2 \pm \text{SD}$)	Glaucoma Patients (n=40) (Mean in $\text{mm}^2 \pm \text{SD}$)	P*
Overall global	1.914 \pm 0.400	1.269 \pm 0.379	<0.0005*
Superior quadrant	0.562 \pm 0.141	0.355 \pm 0.133	<0.0005*
Temporal quadrant	0.324 \pm 0.084	0.260 \pm 0.090	0.024*
Inferior quadrant	0.564 \pm 0.150	0.321 \pm 0.112	<0.0005*
Nasal quadrant	0.464 \pm 0.123	0.334 \pm 0.132	0.002*
ST sector	0.275 \pm 0.075	0.171 \pm 0.081	<0.0005*
IT sector	0.261 \pm 0.077	0.137 \pm 0.063	<0.0005*
SN sector	0.287 \pm 0.075	0.183 \pm 0.067	<0.0005*
IN sector	0.303 \pm 0.085	0.183 \pm 0.069	<0.0005*

Note: *Significantly different ($P < 0.05$) values.

Abbreviations: MDB, minimum distance band; SD, standard deviation; ST, superior-temporal; IT, inferior-temporal; SN, superior-nasal; IN, inferior-nasal.

except for the temporal quadrant, had significantly thinner mean measurements for RNFL thickness, rim volume, and rim thickness than for normal subjects (P value range: <0.0005–0.039 [Tables 2 and 4]).

Table 5 shows the CVs for RNFL thickness and the five neuroretinal rim parameters for all study participants. For each region of interest within a given participant group, MDB thickness had lower CVs than all other neuroretinal rim parameters (eg, global MDB thickness CVs of 2.4% and 3.6% [Table 5] versus CVs of 3.0% [rim volume, Table 5] and 18.9% [rim area, Table 5] for the other global neuroretinal rim parameters). Global MDB thickness and global RNFL thickness were similarly reproducible for normal and glaucoma patients (eg, global MDB thickness CVs 2.4% and 3.6% [Table 5] and global RNFL thickness CVs 1.3% and 2.2% [Table 5], $P > 0.05$ for both comparisons). Reproducibility of MDB thickness was lower in glaucoma patients for the superior and inferior quadrants compared to normal subjects (CVs of 9.6% versus 3.4% and 6.9% versus

Table 4 Spectralis Optical Coherence Tomography Neuroretinal Rim Measurements in Normal versus Glaucomatous Eyes

Reference-plane Dependent Neuroretinal Rim Measurements			
Rim Area			
Region of Interest	Normal Patients (n=27) (Mean in mm ² ± SD)	Glaucoma Patients (n=40) (Mean in mm ² ± SD)	P*
Overall global	1.522 ± 0.508	0.892 ± 0.384	<0.0005*
Superior quadrant	0.425 ± 0.150	0.254 ± 0.122	<0.0005*
Temporal quadrant	0.274 ± 0.170	0.143 ± 0.080	0.001*
Inferior quadrant	0.433 ± 0.142	0.243 ± 0.127	<0.0005*
Nasal quadrant	0.389 ± 0.108	0.252 ± 0.129	0.001*
ST sector	0.203 ± 0.085	0.111 ± 0.058	<0.0005*
IT sector	0.207 ± 0.081	0.102 ± 0.069	<0.0005*
SN sector	0.222 ± 0.070	0.142 ± 0.074	0.001*
IN sector	0.226 ± 0.072	0.141 ± 0.067	<0.0005*
Rim Volume			
Region of Interest	Normal Patients (n=27) (Mean in mm ³ ± SD)	Glaucoma Patients (n=40) (Mean in mm ³ ± SD)	P*
Overall global	0.249 ± 0.204	0.094 ± 0.090	0.001*
Superior quadrant	0.073 ± 0.063	0.027 ± 0.027	0.002*
Temporal quadrant	0.029 ± 0.048	0.011 ± 0.016	0.092
Inferior quadrant	0.087 ± 0.060	0.026 ± 0.023	<0.0005*
Nasal quadrant	0.060 ± 0.043	0.029 ± 0.036	0.013*
ST sector	0.036 ± 0.035	0.012 ± 0.014	0.003*
IT sector	0.040 ± 0.033	0.010 ± 0.011	<0.0005*
SN sector	0.038 ± 0.029	0.016 ± 0.014	0.002*
IN sector	0.047 ± 0.029	0.017 ± 0.014	<0.0005*
Rim Thickness			
Region of Interest	Normal Patients (n=27) (Mean in µm ± SD)	Glaucoma Patients (n=40) (Mean in µm ± SD)	P*
Overall global	152.2 ± 67.9	94.5 ± 58.3	0.005*
Superior quadrant	159.2 ± 73.8	97.6 ± 68.4	0.008*
Temporal quadrant	86.6 ± 57.8	64.6 ± 49.3	0.099
Inferior quadrant	188.9 ± 82.1	102.0 ± 51.9	<0.0005*
Nasal quadrant	148.9 ± 84.9	95.5 ± 77.2	0.039*
ST sector	156.5 ± 74.2	89.8 ± 72.0	0.005*
IT sector	174.9 ± 82.7	88.0 ± 52.0	<0.0005*
SN sector	161.2 ± 76.9	100.5 ± 70.5	0.01*
IN sector	201.3 ± 89.0	107.5 ± 58.5	<0.0005*

Note: *Significantly different (P<0.05) values.

Abbreviations: SD, standard deviation; ST, superior-temporal; IT, inferior-temporal; SN, superior-nasal; IN, inferior-nasal.

Table 5 Coefficient of Variation (CV) for Spectralis Optical Coherence Tomography Retinal Nerve Fiber Layer (RNFL) Thickness and Neuroretinal Rim Measurements in Normal versus Glaucomatous Eyes

Normal Patients (n=27)						
Region of Interest	RNFL Thickness	Neuroretinal Rim				
		MDB Thickness	MDB Area	Rim Area	Rim Volume	Rim Thickness
Overall global	1.3%	2.4%	4.3%	8.7%	3.0%	7.7%
Superior quadrant	2.1%	3.4%	10.2%	12.4%	10.0%	8.7%
Temporal quadrant	2.4%	5.1%	9.7%	23.0%	11.0%	16.5%
Inferior quadrant	1.8%	2.7%	6.9%	9.9%	7.0%	6.9%
Nasal quadrant	2.2%	2.7%	11.8%	7.2%	9.6%	7.0%
ST sector	2.1%	4.0%	11.8%	15.3%	11.5%	10.0%
IT sector	1.8%	4.0%	10.0%	13.5%	11.5%	10.4%
SN sector	2.6%	4.0%	13.5%	12.3%	14.5%	11.4%
IN sector	2.3%	4.0%	9.3%	11.7%	11.1%	8.4%
Glaucoma Patients (n=40)						
Region of Interest	RNFL Thickness	Neuroretinal Rim				
		MDB Thickness	MDB Area	Rim Area	Rim Volume	Rim Thickness
Overall global	2.2%	3.6%	5.4%	18.9%	14.6%	10.1%
Superior quadrant	2.9%	9.6%	14.8%	24.6%	24.9%	16.7%
Temporal quadrant	3.0%	5.1%	9.2%	37.3%	50.6%	15.6%
Inferior quadrant	3.2%	6.9%	12.5%	36.2%	15.8%	11.8%
Nasal quadrant	4.2%	3.0%	9.6%	13.2%	11.0%	9.2%
ST sector	3.7%	9.7%	19.4%	33.2%	33.4%	15.8%
IT sector	4.2%	9.5%	15.8%	52.2%	19.9%	17.1%
SN sector	4.1%	12.4%	20.6%	20.3%	27.6%	20.6%
IN sector	4.0%	8.0%	14.6%	29.4%	18.5%	11.7%

Notes: Reproducibility is expressed by the CV. The CV is the ratio of the standard deviation over the mean, where the standard deviation corresponds to the residual standard error from a regression model adjusting for patient and an indicator for each measurement.

Abbreviations: CV, coefficient of variation; RNFL, retinal nerve fiber layer; MDB, minimum distance band; ST, superior-temporal; IT, inferior-temporal; SN, superior-nasal; IN, inferior-nasal.

2.7%; $P < 0.05$, respectively). There were no statistically significant differences between normal and glaucoma patients for RNFL thickness in the four quadrants. Nevertheless, it is noted that normal patients had lower CVs than glaucoma patients in 50 out of 54 comparisons (ie, for all but 3 combinations of the 6 parameters and 9 regions of interest), though this difference was statistically significant for 19 comparisons at the 0.05 level. Additionally, global CVs were either the lowest or second lowest among all regions for all parameters and for both patient groups.

Table 6 shows the ICCs for RNFL thickness and the five neuroretinal rim parameters for all study participants. Among the measured parameters (MDB thickness, MDB area, rim volume, rim area, rim thickness, RNFL thickness), the ICCs for global MDB thickness and global RNFL thickness were both greater than 0.98 in normal and

Table 6 Intraclass Correlation Coefficient (ICC) [95% CI] for Spectralis Optical Coherence Tomography Retinal Nerve Fiber Layer (RNFL) Thickness and Neuroretinal Rim Measurements in Normal versus Glaucomatous Eyes

Normal Patients (n=27)						
Region of Interest	RNFL Thickness	Neuroretinal Rim				
		MDB Thickness	MDB Area	Rim Area	Rim Volume	Rim Thickness
Overall global	0.993 (0.987–0.997)	0.981 (0.960–0.991)	0.957 (0.909–0.980)	0.928 (0.850–0.966)	0.999 (0.997–0.999)	0.967 (0.929–0.985)
Superior quadrant	0.984 (0.969–0.992)	0.966 (0.928–0.984)	0.852 (0.703–0.929)	0.888 (0.771–0.947)	0.987 (0.973–0.994)	0.965 (0.926–0.984)
Temporal quadrant	0.989 (0.978–0.994)	0.947 (0.889–0.975)	0.847 (0.695–0.927)	0.842 (0.686–0.924)	0.994 (0.988–0.997)	0.939 (0.872–0.972)
Inferior quadrant	0.992 (0.985–0.996)	0.979 (0.956–0.991)	0.935 (0.865–0.970)	0.913 (0.819–0.959)	0.990 (0.978–0.995)	0.973 (0.942–0.988)
Nasal quadrant	0.989 (0.980–0.995)	0.978 (0.952–0.990)	0.824 (0.654–0.915)	0.937 (0.868–0.971)	0.982 (0.962–0.992)	0.985 (0.967–0.993)
ST sector	0.980 (0.963–0.990)	0.959 (0.912–0.981)	0.834 (0.672–0.920)	0.878 (0.752–0.942)	0.986 (0.971–0.994)	0.958 (0.911–0.980)
IT sector	0.989 (0.979–0.995)	0.966 (0.927–0.984)	0.893 (0.782–0.950)	0.889 (0.774–0.948)	0.982 (0.962–0.992)	0.952 (0.899–0.978)
SN sector	0.985 (0.972–0.993)	0.953 (0.901–0.978)	0.769 (0.559–0.887)	0.862 (0.724–0.935)	0.965 (0.925–0.984)	0.940 (0.873–0.972)
IN sector	0.994 (0.989–0.997)	0.955 (0.904–0.979)	0.899 (0.792–0.952)	0.877 (0.751–0.942)	0.968 (0.932–0.985)	0.962 (0.919–0.982)
Glaucoma Patients (n=40)						
Region of Interest	RNFL Thickness	Neuroretinal Rim				
		MDB Thickness	MDB Area	Rim Area	Rim Volume	Rim Thickness
Overall global	0.992 (0.986–0.995)	0.983 (0.967–0.991)	0.969 (0.942–0.983)	0.819 (0.684–0.899)	0.977 (0.957–0.988)	0.973 (0.950–0.986)
Superior quadrant	0.990 (0.984–0.995)	0.915 (0.845–0.954)	0.860 (0.751–0.923)	0.761 (0.594–0.866)	0.938 (0.886–0.967)	0.943 (0.895–0.969)
Temporal quadrant	0.986 (0.977–0.992)	0.969 (0.943–0.984)	0.933 (0.878–0.964)	0.619 (0.387–0.778)	0.884 (0.793–0.937)	0.956 (0.919–0.977)
Inferior quadrant	0.989 (0.981–0.994)	0.950 (0.908–0.973)	0.880 (0.786–0.935)	0.623 (0.392–0.781)	0.968 (0.941–0.983)	0.948 (0.905–0.972)
Nasal quadrant	0.985 (0.975–0.992)	0.992 (0.985–0.996)	0.941 (0.892–0.968)	0.929 (0.871–0.962)	0.992 (0.985–0.996)	0.987 (0.975–0.993)
ST sector	0.985 (0.975–0.992)	0.930 (0.872–0.962)	0.848 (0.731–0.916)	0.662 (0.447–0.805)	0.923 (0.860–0.958)	0.962 (0.929–0.980)
IT sector	0.988 (0.980–0.993)	0.940 (0.890–0.968)	0.884 (0.793–0.937)	0.548 (0.290–0.731)	0.966 (0.938–0.982)	0.921 (0.856–0.957)
SN sector	0.987 (0.978–0.993)	0.846 (0.729–0.915)	0.731 (0.547–0.848)	0.847 (0.730–0.916)	0.916 (0.848–0.955)	0.915 (0.846–0.954)
IN sector	0.984 (0.972–0.991)	0.929 (0.871–0.962)	0.862 (0.756–0.925)	0.688 (0.483–0.821)	0.952 (0.912–0.974)	0.955 (0.918–0.976)

Note: Reliability is expressed by the ICC. A one-way ANOVA was used to determine the ICC.

Abbreviations: ICC, intraclass correlation coefficient; CI, confidence interval; RNFL, retinal nerve fiber layer; MDB, minimum distance band; ST, superior-temporal; IT, inferior-temporal; NS, superior-nasal; IN, inferior-nasal.

glaucoma patients (global MDB thickness ICCs 0.981 to 0.983 [Table 6] and global RNFL thickness ICCs 0.992 to 0.993 [Table 6] versus ICCs of 0.819 [global rim area for glaucoma patients, Table 6] to 0.999 [global rim volume for normal subjects, Table 6] for the other four measured parameters). As a general trend for all parameters for the whole study group, reliabilities for global measurements were higher than for quadrant/sector measurements (global ICCs 0.819 [rim area for glaucoma patients, Table 6] to 0.999 [rim volume for normal patients, Table 6] versus quadrants/sectors 0.548 [IT sector rim area for glaucoma patients, Table 6] to 0.994 [IN sector RNFL thickness and temporal quadrant rim volume for normal patients, Table 6]).

Table 7 shows the Sw values for RNFL thickness and the five neuroretinal rim measurements for all study participants. The Sw + 1.96 standard error (se) ranged from 6.9 + 4.5 μ m to 7.5 + 4.1 μ m for global MDB thickness (Table 7) and from 1.2 + 0.2 μ m to 1.5 + 0.5 μ m for global RNFL thickness (Table 7).

Table 7 Within-Subject Variance [$Sw \pm 1.96$ Standard Error (Se)] for Spectralis Optical Coherence Tomography Retinal Nerve Fiber Layer (RNFL) Thickness and Neuroretinal Rim Measurements in Normal versus Glaucomatous Eyes

Normal Patients (n=27)						
Region of Interest	RNFL Thickness (μm)	Neuroretinal Rim				
		MDB Thickness (μm)	MDB Area (mm^2)	Rim Area (mm^2)	Rim Volume (mm^3)	Rim Thickness (μm)
Overall global	1.2 ± 0.2	6.9 ± 4.5	0.084 ± 0.022	0.139 ± 0.079	0.007 ± 0.002	12.5 ± 7.3
Superior quadrant	2.6 ± 1.3	11.0 ± 2.7	0.057 ± 0.016	0.052 ± 0.019	0.007 ± 0.002	13.9 ± 6.5
Temporal quadrant	1.6 ± 0.4	11.6 ± 3.9	0.034 ± 0.008	0.071 ± 0.032	0.004 ± 0.002	14.5 ± 7.1
Inferior quadrant	2.1 ± 0.5	9.1 ± 3.1	0.039 ± 0.014	0.043 ± 0.017	0.006 ± 0.003	13.6 ± 5.1
Nasal quadrant	1.5 ± 0.3	8.0 ± 3.5	0.054 ± 0.023	0.028 ± 0.006	0.006 ± 0.003	10.5 ± 6.3
ST sector	2.9 ± 1.2	12.8 ± 3.1	0.032 ± 0.007	0.031 ± 0.014	0.004 ± 0.001	15.4 ± 4.5
IT sector	2.5 ± 0.6	12.4 ± 3.1	0.026 ± 0.008	0.028 ± 0.020	0.005 ± 0.002	18.3 ± 7.6
SN sector	2.8 ± 1.2	13.4 ± 4.1	0.038 ± 0.009	0.027 ± 0.011	0.006 ± 0.003	19.2 ± 9.8
IN sector	2.4 ± 0.5	14.0 ± 7.4	0.028 ± 0.010	0.026 ± 0.008	0.005 ± 0.001	17.6 ± 10.8
Glaucoma Patients (n=40)						
Region of Interest	RNFL Thickness (μm)	Neuroretinal Rim				
		MDB Thickness (μm)	MDB Area (mm^2)	Rim Area (mm^2)	Rim Volume (mm^3)	Rim Thickness (μm)
Overall global	1.5 ± 0.5	7.5 ± 4.1	0.067 ± 0.013	0.171 ± 0.090	0.014 ± 0.011	9.6 ± 3.1
Superior quadrant	2.4 ± 0.7	21.6 ± 14.3	0.052 ± 0.022	0.063 ± 0.027	0.007 ± 0.005	16.6 ± 5.9
Temporal quadrant	1.8 ± 0.6	9.1 ± 2.4	0.024 ± 0.005	0.055 ± 0.017	0.006 ± 0.005	10.4 ± 2.9
Inferior quadrant	2.5 ± 0.6	14.7 ± 4.9	0.040 ± 0.012	0.087 ± 0.034	0.004 ± 0.001	12.0 ± 2.9
Nasal quadrant	2.3 ± 0.6	6.4 ± 1.4	0.033 ± 0.014	0.035 ± 0.014	0.003 ± 0.002	8.9 ± 2.4
ST sector	3.3 ± 0.9	21.2 ± 12.2	0.033 ± 0.008	0.037 ± 0.014	0.004 ± 0.003	14.2 ± 4.3
IT sector	3.5 ± 0.9	18.2 ± 6.7	0.022 ± 0.007	0.053 ± 0.022	0.002 ± 0.001	14.9 ± 5.3
SN sector	3.0 ± 0.9	28.8 ± 17.4	0.037 ± 0.011	0.030 ± 0.012	0.004 ± 0.003	21.0 ± 8.6
IN sector	2.9 ± 0.9	18.4 ± 7.8	0.027 ± 0.010	0.041 ± 0.017	0.003 ± 0.001	12.5 ± 3.5

Note: Sw is defined as the square root of the within-subject variance, defined as the within-subject sum of squares divided by its degrees of freedom.

Abbreviations: Sw, within-subject standard deviation; se, standard error; RNFL, retinal nerve fiber layer; MDB, minimum distance band; ST, superior-temporal; IT, inferior-temporal; SN, superior-nasal; IN, inferior-nasal.

Discussion

This study is the first comprehensive evaluation of the reproducibility of five neuroretinal rim SDOCT parameters (two reference-plane independent [3D MDB thickness and 3D MDB area] and three reference-plane dependent [3D rim volume, 2D rim area, and 2D rim thickness] neuroretinal rim measurements) using the Spectralis SDOCT instrument.

Among the five neuroretinal rim parameters (MDB thickness, MDB area, rim area, rim volume, and rim thickness), MDB thickness had the lowest CVs among all regions of interest (eg, global MDB thickness CVs of 2.4% and 3.6% [Table 5] versus global CVs 3.0% and 18.9% for the other four neuroretinal rim parameters [Table 5]). For normal and glaucoma patients, RNFL thickness and MDB thickness had similar reproducibility (eg, global RNFL thickness CVs 1.3% and 2.2% [Table 5] versus global MDB thickness CVs 2.4% and 3.6% [Table 5], $P > 0.05$ for both comparisons). Reproducibility of MDB thickness was lower in glaucoma patients for the superior and inferior quadrants compared to normal subjects (9.6% versus 3.4% and 6.9% versus 2.7%; $P < 0.05$, respectively). Given the study findings, 3D MDB neuroretinal rim thickness and 2D RNFL thickness measurements are reproducible, and both may be useful complementary tools for glaucoma diagnosis and monitoring in clinical practice.

Clinically, this translates to an expected global MDB neuroretinal rim thickness test–retest variability of 2.4% (Table 5) with the Sw of $6.9 \pm 4.5 \mu\text{m}$ (Table 7) in normal patients, and 3.6% (Table 5) with the Sw of $7.5 \pm 4.1 \mu\text{m}$ (Table 7) in glaucoma patients. Similarly, global BMO-MRW test–retest variability goes from 0.85% to 1.17% with the Sw from 2.88 to 2.98 μm in normal patients, and from 1.19% to 3.07% with the Sw from 2.24 to 3.70 μm in glaucoma patients.^{5,9,23}

Among the five neuroretinal rim parameters (MDB thickness, MDB area, rim area, rim volume, and rim thickness) for normal and glaucoma patients, MDB thickness had the lowest CV percentages for all regions of interest (eg, global MDB thickness CVs 2.4% and 3.6% [Table 5] versus CVs 3.0% [rim volume] and 18.9% [rim area] for the other four global neuroretinal rim parameters [Table 5]). This study is unique because it is the first to compare reproducibility between reference-plane independent and reference-plane dependent neuroretinal rim parameters. We would expect MDB thickness to have better reproducibility than reference-plane dependent parameters (rim volume, rim area, rim thickness), as our data suggest, because MDB thickness directly measures the neuroretinal rim in 3D space using the ILM and RPE/BM as anatomic landmarks. In contrast, reference plane dependent neuroretinal rim parameters (rim area, rim volume, rim thickness) are likely to be more variable than MDB thickness, because these parameters quantify neuroretinal rim tissue along an arbitrarily defined flat reference plane 150 μm above the RPE/BM.^{4,7,24} This causes variation, because the reference plane can differ between individual patients as well as within individual patient scans on different days due to variation of the retinal optic nerve and RNFL topography despite using the follow-up function to limit errors.^{24,25} While no previous studies have compared MDB thickness reproducibility versus MDB area reproducibility, the reference plane-independent BMO-MRW parameter, which is a similar 3D neuroretinal rim glaucoma parameter, has shown better reproducibility than BMO-minimum rim area (BMO-MRA) in normal and glaucoma patients (global BMO-MRW CVs of 0.85–3.07% versus global BMO-MRA CVs 2.2–4.08%).^{5,9,23,26} Similarly, our study found global MDB thickness CVs to be less variable than global MDB area CVs in normal and glaucoma patients (eg, global MDB thickness CVs 2.4% and 3.6% [Table 5] versus MDB area CVs 4.3% and 5.4% [Table 5]).

MDB thickness and RNFL thickness had similar reproducibility in normal and glaucoma patients, though MDB thickness was lower in glaucoma patients for the superior and inferior quadrants compared to normal subjects (CVs of 9.6% versus 3.4% and 6.9% versus 2.7%; $P < 0.05$, respectively). There are currently no other studies in the literature which directly compare reproducibility between RNFL thickness and MDB thickness. Nevertheless, this paper's findings align with previous literature that has demonstrated similar reproducibility for *global* BMO-MRW and *global* RNFL thickness in normal and glaucoma patients (global BMO-MRW CVs 0.85–3.07% versus global RNFL thickness CVs 0.5–5.3%).^{5,9,12,15,16,21,23,27} Previous studies by our group have shown that MDB thickness has similar or better diagnostic capability as RNFL thickness.^{4,6,7} This study further illustrates that MDB thickness has a similar reproducibility as RNFL thickness, the most commonly used parameter for glaucoma.

Our data suggest that normal patients have less variable MDB thickness and RNFL thickness measurements compared to glaucoma patients, because normal patients had lower CVs in 50 out of 54 comparisons, (ie, for all but 3 combinations of the 6 parameters and 9 regions of interest), though this difference was statistically significant for 19 comparisons at the 0.05 level. This finding agrees with the literature for BMO-MRW reproducibility that demonstrated lower variability for normal eyes compared to glaucomatous eyes (global BMO-MRW CVs 0.85–1.17% in normal patients versus global BMO-MRW CVs 1.19–3.07% in glaucoma patients).^{5,9,23} Likewise, previous studies have shown better reproducibility for RNFL thickness among normal patients compared to glaucoma patients (eg, global RNFL thickness CVs 0.3–5.0% in normal patients versus

global RNFL thickness 0.9–5.3% in glaucoma patients).^{10–12,15,16,21,27–30} Töteberg-Harms et al¹⁵ suggests that glaucomatous eyes may be more variable than normal eyes due to less stable ocular fixation, which makes it more difficult for OCT measurements to be derived from the exact same position around the disc.¹⁵ MDB thickness measurements for glaucoma patients may be more variable than for normal patients because the glaucoma MDB thickness measurements were much thinner than those of normal participants (P value range: <0.0005 – 0.024 [Tables 3 and 4]), making it more difficult for the MDB algorithm to correctly measure the thickness of the nerve tissue at the optic nerve.¹⁵ Glaucoma patients also have thinner RNFL thickness measurements compared to normal patients, and glaucoma-related loss of RNFL reflectivity may contribute to errors in RNFL segmentation.¹⁵ Moreover, Budenz et al²¹ noted that higher CVs in glaucomatous eyes compared to normal eyes should be expected even if measurement variability was similar between the two groups, because the CV is calculated by dividing the standard deviation by the mean MDB thickness measurement, which is thinner for glaucoma patients.²¹ We are also unable to determine how much variability in glaucomatous eyes may be due to the variability in disease stages for the glaucoma group.

MDB thickness measurements were similar for global values and quadrants/sectors (global CVs 2.4% and 3.6% [Table 5] versus quadrants/sectors CVs 2.7% and 12.4% [Table 5]), though MDB thickness for the superior and inferior quadrants is less significantly reproducible among glaucoma subjects. However, it is noteworthy that out of 12 parameter-patient groups (eg, RNFL thickness in normal patients, MDB thickness in normal patients, etc), the global CV was the lowest among all regions for 6 of the groups. Park et al⁵ and Reis et al⁹ found that global BMO-MRW had the best reproducibility among all regions for normal and glaucoma patients (global BMO-MRW CVs 0.87–3.07% versus quadrant/sector BMO-MRW CVs 1.5–12.6%).^{5,9} Previous studies also found that global RNFL thickness had better reproducibility than quadrants/sectors (global RNFL thickness CVs of 0.3–5.3% versus quadrant/sector CVs of 0.5–11.9%).^{11,12,15,16,27} Quadrant and sector regions can have higher variability than the global region, because quadrant and sector measurements are impacted more by regional imaging artifacts, algorithm performance, and smaller sample size, whereas larger global region measurements are derived from averaging different sector variabilities.^{5,12} Gurses-Ozden et al³¹ demonstrated that reproducibility could be improved by averaging and increasing sample density, showing that larger regions are less variable because more individual measurements contribute to the mean.³¹

Our study has limitations. For one, glaucoma patients were older than normal subjects by an average of 13.3 years (P value <0.0005 [Table 1]). In addition, both normal and glaucoma subjects had wide age ranges as indicated by the standard deviations, which were 15.1 years for normal participants and 9.4 years for glaucoma participants. Some studies have shown that global MDB thickness and global BMO-MRW decline with advancing age.^{6,32} Thus, this age disparity may have influenced parameter variabilities for both normal and glaucoma participant groups. Secondly, the study included glaucoma patients as defined by the inclusion criteria but did not stratify based on glaucoma stage. Park et al⁵ noted that BMO-MRW measurement variability was worse in more advanced glaucoma, which may also be true of the five neuroretinal measurements. Thirdly, the study included only glaucoma patients with existing VF defects, making the results ungeneralizable to subjects with pre-perimetric glaucoma.

Our study illustrates that 3D MDB neuroretinal rim thickness has similar reproducibility in glaucoma and normal groups as the most commonly used glaucoma OCT parameter, peripapillary RNFL thickness; however, MDB thickness for the superior and inferior quadrants is less reproducible among glaucoma subjects. The data further suggest that MDB thickness has better reproducibility than other neuroretinal rim parameters (MDB area, rim area, rim volume, rim thickness). Previous studies have demonstrated that MDB thickness has similar or better diagnostic capability for glaucoma compared to RNFL thickness.^{4,6,7} Taken together with our study, these findings suggest that the high-density 3D MDB neuroretinal rim thickness parameter may be a promising clinical tool for diagnosing glaucoma and monitoring glaucomatous disease progression. Therefore, new high-density 3D algorithms should be incorporated into commercially available SDOCT machines to improve the care of glaucoma patients.

Abbreviations

2D, two-dimensional; RNFL, retinal nerve fiber layer; 3D, three-dimensional; SDOCT, spectral domain optical coherence tomography; MDB, minimum distance band; Sw, within-subject variance; CV, coefficient of variation; ICC, intraclass correlation coefficient; BMO-MRW, Bruch's membrane opening-minimum rim width; AUROC, area under the receiver

operating characteristic curve; RPE/BM, retinal pigment epithelium/Bruch's membrane complex; BMO, Bruch's membrane opening; MEE, Massachusetts Eye and Ear; SIG, SDOCT in Glaucoma; VF, visual field; OCT, optical coherence tomography; IOP, intraocular pressure; IN, inferior-nasal; SN, superior-nasal; IT, inferior-temporal; ST, superior-temporal; ILM, internal limiting membrane; MD, mean deviation; BMO-MRA, Bruch's membrane opening-minimum rim area.

Data Sharing Statement

Data are available, upon request, from the corresponding author, Teresa C. Chen, MD.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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