Relationship between Visual Field Sensitivity and Macular Ganglion Cell Complex Thickness as Measured by Spectral-Domain Optical Coherence Tomography

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Purpose. To evaluate the strength and pattern of the relationship between visual field (VF) mean sensitivity (MS), assessed by standard automated perimetry (SAP), and macular ganglion cell complex thickness (GCCT), measured with spectral-domain optical coherence tomography (SD-OCT).

Methods. Ninety-seven glaucoma patients were enrolled. GCCT, determined by ganglion cell complex (GCC) scanning, and two peripapillary retinal nerve fiber layer thickness (pRNFLT) measurements, using the NHM4 (RNFL1) and RNFL 3.45 (RNFL2) modes, were recorded. MS was recorded on the decibel (dB) and 1/L scales. The relationship between function (MS) and structure (GCC, pRNFLT) was sought.

Results. The association of MS (in decibels) with GCC global ($r = 0.445$) and sectoral (superior, $r = 0.528$; inferior, $r = 0.370$) thicknesses was not significantly different from that of MS to global (RNFL1, $r = 0.505$; RNFL2, $r = 0.498$) and sectoral (RNFL 1 superior, $r = 0.559$; inferior, $r = 0.440$; RNFL 2 superior, $r = 0.535$; inferior, $r = 0.443$) pRNFLT, on linear regression analysis. The relationship pattern was curvilinear on the dB scale against GCCT and RNFLT. Logarithmic regression of MS (using both the dB and 1/L scales) against GCCT and RNFLT was better than linear regression in describing the pattern of association.

Conclusions. GCCT, determined by SD-OCT, showed correlation to MS of a strength similar to that demonstrated between MS and pRNFLT. (*Invest Ophthalmol Vis Sci.* 2010;51: 6401–6407) DOI:10.1167/iovs.09-5035

Glaucomatous damage occurs in retinal ganglion cells (RGCs) and their axons, leading to characteristic changes in the structure of the optic disc and retinal nerve fiber layer (RNFL). Such structural damage influences the visual function of the glaucoma patient.[1] RGC loss cannot be easily detected on routine fundus examination with a 90-D lens. Thus, glaucoma diagnosis is principally based on characteristic optic disc or peripapillary RNFL (pRNFL) changes and the corresponding visual field (VF) defects. However, as the structural loss of RGCs often precedes the functional glaucomatous VF defects,[2–5] various structural imaging devices have been developed to offer reliable detection of glaucoma when the condition is at the preperimetric stage.[6–8]

If a tool is to be useful for glaucoma diagnosis and for tracking disease progression, the glaucomatous structure–function relationship must be tested and validated in new imaging devices, as such validation provides the practical means necessary to predict the behavior of the VF with respect to changes in optic nerve heads in the course of disease progression. The validation must be performed in a cross-sectional manner. The relationship between structure (pRNFL thickness; pRNFLT) and function (differential light sensitivity; DLS) has been found to be curvilinear when DLS is expressed on the decibel (dB) scale, whereas function appears to be linearly related to structure when DLS is expressed on a nonlogarithmic DLS scale.[9–13]

In the time since the introduction of optical coherence tomography (OCT) by Huang et al.,[14] the technique has been useful for measuring pRNFLT and macular thickness in detecting glaucoma and for monitoring disease progression.[15–20] Furthermore, in several studies, time-domain (TD) OCT had provided high correlations between VF sensitivity and pRNFLT in glaucoma patients.[21–23] For example, Leung et al.[21] showed that the coefficient of correlation between VF mean deviation (MD) and average pRNFLT was 0.79. The RTVue-100 OCT (Optovue Inc., Fremont, CA) is a newer OCT instrument incorporating spectral domain (SD) technology, providing higher scan resolution and speed than is possible with TD-OCT. It includes a ganglion cell complex (GCC) scanning mode that measures GCC thickness (GCCT) from the internal limiting membrane to the inner nuclear layer, composed of ganglion cell axons, cell bodies, and dendrites. The device also permits two forms of pRNFLT measurement, one of which involves direct circumpapillary scanning and the other, resampling from en face imaging.

To the best of our knowledge, glaucomatous structure–function relationships assessed by GCCT derived from SD-OCT and standard automated perimetry (SAP) parameters have not been investigated. Thus, in the present study, we evaluated the strength and pattern of the relationship between VF sensitivity and RNFLT using the GCC and peripapillary modes of SD-OCT.

Methods

Subjects

All glaucoma subjects were recruited prospectively, in a consecutive manner, from the glaucoma clinic of the Asan Medical Center, Seoul, Korea. At initial evaluation, each subject underwent a complete ophthalmic examination, including medical, ocular, and family histories; visual acuity (VA) testing; visual field perimetry (Humphrey Field Analyzer [HFA]; Swedish Interactive Threshold Algorithm (SITA) 24-2 test; Carl Zeiss Meditec, Dublin, CA); multiple intraocular pressure

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(IOP) measurements by Goldmann applanation tonometry (GAT); stereoscopic optic nerve head photography; and SD-OCT scanning (RTVue-100; Optovue). All patients with glaucoma had had more than one experience with visual field perimetry testing. To minimize the learning effect, only the second perimetric test was used in the analysis. For inclusion in the study, all participants had to meet the following criteria: best-corrected VA of 20/30 or better, with a spherical equivalent within ±5 D and a cylinder correction within +3 D; presence of a normal anterior chamber and open-angle on slit lamp and gonioscopic examinations; and reliable visual field test results with a false-positive error <15%, a false-negative error <15%, and fixation loss <20%. Subjects with any other ophthalmic or neurologic condition that could result in visual field defects, with a history of any intraocular surgery or with a history of diabetes mellitus, were excluded.

Glaucomatous eyes were defined as having VF defects, as confirmed by at least two reliable VF examinations and the presence of a compatible glaucomatous optic disc that showed increased cupping (a vertical cup-disc [C/D] ratio >0.6), a difference in vertical C/D ratio of >0.2 between eyes, diffuse or focal neural rim thinning, disc hemorrhage, or RNFL defects. Eyes with glaucomatous VF defects were defined as those with a cluster of three points with probabilities of <5% on the pattern deviation map in at least one hemifield, including at least one point with a probability of <1%; a cluster of two points with a probability of <1% and a glaucoma hemifield test (GHT) result outside 97% of age-specific normal limits; or a pattern standard deviation (PSD) outside 95% of normal limits. One eye was randomly selected if both eyes were found to be eligible for the study.

Mean sensitivity (MS) was evaluated by SAP (HFA; Carl Zeiss Meditec, Inc.). MS was expressed in two ways: decibel (dB) and nonlogarithmic 1/L scales (L; luminance measured in lamberts). The DLS at each tested location can be simply written as DLS (dB) = $10 \times \log_{10}$ (1/L). The nonlogarithmic 1/L value at each tested location was calculated by dividing the decibel reading by 10 followed by derivation of the antilogarithm. Two test points next to the blind spot were excluded from analysis. The global MS was defined as the average value of the DLS obtained at each test point. The superior retinal MS associated with the inferior hemiretinal GCCT and pRNFLT measurements was calculated using data from 26 test points in the superior hemifield, and the inferior retinal MS referable to superior hemiretinal GCCT and pRNFLT test data was calculated from data at 26 test points in the inferior hemifield. The details of MS calculation have been described elsewhere.[24]

All participants gave written informed consent before enrollment. All procedures conformed to the Declaration of Helsinki, and the study was approved by the Institutional Review Board of the Asan Medical Center, University of Ulsan, Seoul, Korea.

Optical Coherence Tomography

The GCC scan protocol was used to obtain GCCT data, and SD-OCT (RTVue-100 OCT; Optovue; running software ver. A4.0.0.143), performed in both the NHM4 (RNFL1) and RNFL 3.45 (RNFL2) scanning modes, was used to determine pRNFLT. Each GCC scan was centered 1 mm temporal to the fovea and covered a region of 7 × 7 mm. The RTVue-100 RNFL 3.45 mode measures RNFLT along a 3.45-mm diameter circle around the optic disc, as does the fast RNFL mode of the Stratus OCT (Carl Zeiss Meditec, Inc.). The RTVue-100 NHM4 mode assesses RNFLT by recalculating data along a circle of 3.45-mm diameter around the optic disc using a map created from en face imaging with 6 circular and 12 linear data inputs. Average, superior, and inferior hemiretinal GCCT data and information from the two modes of pRNFLT measurement, were used in the analysis. Any images with a signal strength index (SSI) less than 40 or showing overt misalignment of the surface-detection algorithm on at least 10% of consecutive A-scans or 15% of cumulative A-scans, or with overt decentration of the measurement circle location (assessed subjectively) were excluded from the analysis. Pharmacologic dilation was performed in all participants, to optimize image quality and retinal segmentation.

According to the criteria described earlier, 11 of 108 eyes that qualified for initial inclusion were excluded because of poor image quality. Eight of these eyes had SSIs less than 40, and three eyes showed overt misalignment of the surface detection algorithm; three eyes were disqualified by both criteria. The final analysis thus included the remaining 97 glaucomatous eyes.

Statistical Analysis

VF MS was treated as the dependent variable and RNFLT as the independent variable in all regressions assessing the structure–function relationship. VF MS was recorded using both the dB and the 1/L scales. As decibel values are a logarithmic transformation of DLS, logarithmic regression was arbitrarily chosen for comparison with linear regression. Therefore, these relationships between average thickness as measured by the GCC and RNFL modes and VF MS were evaluated using both linear ($y = a + bx$) and logarithmic ($y = a + b\log_{10}x$) regression analyses. To measure the degree of association between, on the one hand, RNFLT, using data obtained from both GCC and peripapillary RNFL modes and VF MS on the other hand, we calculated Pearson's correlation coefficients (r) for the global and sectoral measurements. To compare the strength of association between RNFLT by using data obtained from both GCC and peripapillary RNFL modes, and VF MS on the other hand, we examined any two correlation coefficients for a statistically significant difference using the bootstrap method (200 replicates). We also compared the global model fit by use of the Akaike information criterion (AIC),[25] which is a measure based on the logarithm of the likelihood function and a low value implying better fit.

All reported P values are two-sided, and $P < 0.05$ indicates statistical significance (SAS, ver. 9.1; SAS Institute, Cary, NC, and MedCalc, ver. 9.6; MedCalc, Mariakerke, Belgium).

Results

Ninety-seven glaucomatous eyes were enrolled in this cross-sectional study. Table 1 lists the patient demographics and biometric parameters. The strength of the relationship between GCCT and RNFLT measured by two different modes (NHM4 and RNFL 3.45) and VF MS expressed in two forms (on the dB and non-logarithmic 1/L scale) are presented in Table 2.

Table 1. Demographics and Clinical Characteristics of the Study Participants

Characteristic	Glaucomatous Eyes (n = 97)
Age, y	55.8 (11.6)
Sex, male:female	42:45
SE, D	−1.2 (2.1)
IOP, mm Hg	16.0 (3.4)
CCT, μm	529.6 (29.4)
C/D ratio	0.73 (0.15)
VF parameters and retinal sensitivity, dB	
MD	−7.0 (5.8)
PSD	6.6 (4.4)
Global MS	22.7 (6.0)
Superior MS	20.3 (8.6)
Inferior MS	25.2 (5.2)
SD-OCT thicknesses, μm	
GCC average	79.37 (9.42)
GCC superior hemiretina	82.85 (10.09)
GCC inferior hemiretina	75.95 (11.76)
NHM4 average	83.90 (12.17)
NHM4 superior hemiretina	86.07 (13.50)
NHM4 inferior hemiretina	81.72 (13.94)
RNFL 3.45 average	83.29 (11.86)
RNFL 3.45 superior hemiretina	86.51 (13.60)
RNFL 3.45 inferior hemiretina	80.12 (13.88)

Data are the mean (SD). SE, spherical equivalent.

TABLE 2. Association between OCT Parameters and HVF MS Expressed on dB and 1/L Scales

Parameter	GCC	RNFL1	RNFL2	GCC vs. RNFL1 *P*	GCC vs. RNFL2 *P*
Average					
DB linear	0.44467	0.50471	0.49754	0.3265	0.3660
DB log	0.45105	0.51624	0.50955	0.2908	0.4308
1/L linear	0.33886	0.37542	0.40462	0.5246	0.2501
1/L log	0.34279	0.37876	0.40979	0.5089	0.3660
Inferior					
DB linear	0.37047	0.44029	0.44339	0.3587	0.3548
DB log	0.38080	0.45251	0.45308	0.3798	0.3632
1/L linear	0.26003*	0.32027	0.37782	0.3319	0.0987
1/L log	0.27102†	0.32784	0.38387	0.3437	0.0920
Superior					
DB linear	0.52757	0.55929	0.53476	0.5330	0.8820
DB log	0.53305	0.57738	0.55273	0.4048	0.7011
1/L linear	0.45021	0.43994	0.45580	0.8426	0.9007
1/L log	0.44692	0.44687	0.46461	0.9992	0.6846

Data are the Pearson correlation coefficient (r) in 97 glaucomatous eyes. Statistical significance, $P < 0.05$. Linear regression, $y = a + bx$; logarithmic regression, $y = a + b \log_{10} x$; inferior, inferior hemiretina; superior, superior hemiretina.

All are $P < 0.001$ except the following: *Inferior I/L linear, GCC: $P < 0.010$; and †Inferior I/L log, GCC: $P < 0.007$.

Our data demonstrate statistically significant associations between GCCT and RNFLT measured by two different modes, and the corresponding MS values, using both linear and logarithmic regression analyses (Table 2, all $P < 0.01$). There were no significant differences in correlation coefficients (indicating the strength of the relationship) between GCCT and RNFLT, measured by either mode, and the corresponding VF MS values (Table 2).

Figures 1 and 2 show the structure–function relationships between average GCCT and RNFLT, measured by the two different SD-OCT modes, and the global MS values expressed in both dB and nonlogarithmic 1/L scales, respectively. Regressions of global VF MS values against average RNFLTs (obtained by GCC, RNFL1, and RNFL 2) were nonlinear when VF MS was expressed on either the dB or nonlogarithmic 1/L scale. Similar patterns of association were noted in both the superior and inferior RNFL sectors.

When VF MS was expressed on either the dB or nonlogarithmic 1/L scale, the AIC values for regressions between VF MS and the RNFLTs derived from the GCC and the two RNFL modes were lower on the logarithmic regression analysis than on linear regression, suggesting that the logarithmic regression model describes the pattern of association more accurately on either scale (Table 3).

DISCUSSION

Greenfield et al.[17] found that TD-OCT macular thickness measurements correlated well with alterations in VF and RNFL structural changes, in patients with moderately advanced glaucoma. They found a strong correlation between mean macular thickness and VF MD ($r^2 = 0.47$; $P < 0.01$) and suggested reduced macular thickness as a surrogate measure of RGC loss in glaucoma.

In the present study, the associations between GCCT and pRNFLT measurements and retinal sensitivity were analyzed based on the default scale of both macular and pRNFL changes, as revealed by SD-OCT, The use of parameters derived from the routine SD-OCT printouts has practical implications in the understanding of structure–function relationships in standard clinical settings. We have demonstrated a significant correlation between SAP and GCCT measurements on glaucomatous eyes, indicating that GCCT measurements are closely associated with functional loss in glaucoma.

For both the global and the two-sector GCCT measurements (inferior and superior hemiretinal thicknesses), Pearson's correlation coefficients describing the relationship between decibel VF sensitivity and GCCT were 0.444, 0.370, and 0.528, respectively. These global and sectoral correlations were not significantly different from the associations between decibel VF sensitivity and pRNFLT (RNFL1, $r = 0.504$, 0.440, and 0.559; RNFL2, $r = 0.498$, 0.443, and 0.535, respectively). The associations between GCCT and pRNFLT measurements and retinal sensitivity, used to identify structure–function relationships, were equally robust. These strong associations held true, regardless of the type of regression (linear versus logarithmic) and the mode of VF expression (MD versus nonlogarithmic 1/L) used, as can be noted in the data of Table 2.

In the present study, many patients had a relatively early stage of glaucoma at the time of the study (mean MD = −7.0 dB). The strength of the structure–function relationships described in Table 2 may have been affected ($r = 0.44$, GCC; $r = 0.50$, RNFL 1 and 2 both for average thickness), because such relationships are stronger in patients with more advanced disease. Leung et al.[26] found that when RNFL thickness was measured with Stratus OCT, the strength of the structure–function relationship remained high ($r^2 = 0.594$) in the moderately advanced glaucoma group (mean MD = −11.1 dB). Conversely, at early stages of glaucoma, the strength of the structure–function relationship has been reported to be low. El Beltagi et al.[27] found a poor correlation between data from the 6 o'clock position and that from the VF zone, corresponding to the inferior nasal step region ($r^2 = 0.01$), when using the Stratus OCT 2000 (Carl Zeiss Meditec, Inc.) to study glaucomatous eyes with early VF defects (mean MD, −1.90 dB).

The strength of a structure–function relationship may also vary depending on the retinal and VF areas in which the association is assessed and possibly with the imaging device used in the study. We did not examine structure–function relationships in smaller regions (for example, by dividing GCC or RNFL data into those from different sectors, including the nasal and temporal areas). More extensive division of pRNFL or GCC data into those from six or eight sectors may have shown a higher degree of structure–function relationship in particular

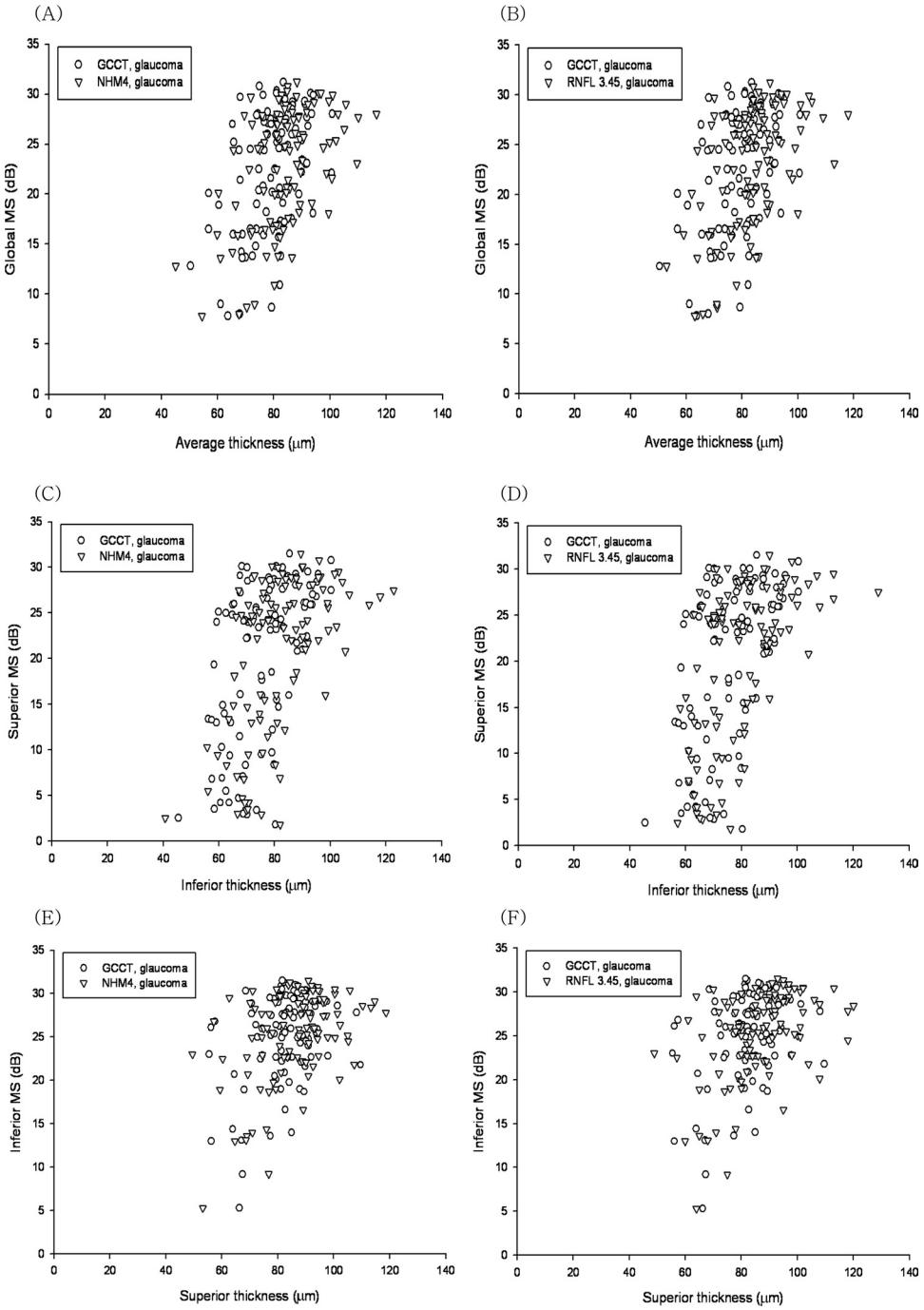

FIGURE 1. Scatter plots showing the associations between SD-OCT thickness parameters and corresponding retinal sensitivities expressed on the dB scale. Average thicknesses versus global MS obtained with the (**A**) GCC and NMH4 and the (**B**) GCC and RNFL 3.45 modes. Inferior average thicknesses versus superior MS obtained in the (**C**) GCC and NMH4 and the (**D**) GCC and RNFL 3.45 modes. Superior average thicknesses versus inferior MS obtained in the (**E**) GCC and NMH4 and the (**F**) GCC and RNFL 3.45 modes.

sectors. Reus and Lemij[9] found, using GDx VCC (Carl Zeiss Meditec, Inc.) data collected from multiple sectors around the optic nerve head, that pRNFLT correlated well with functional loss in glaucomatous subjects, particularly in the superotemporal sector ($r = 0.77$). However, the correlation was poor in the temporal sector ($r = 0.19$). Other studies have also found low correlations between RNFLT measurements obtained by scanning laser polarimetry (SLP) in the nasal and temporal sectors and the corresponding visual sensitivities.[10–13] The lack of a relationship in these areas has been explained by the presence of a low signal-to-noise ratio, as well as by a lack of adjustment for spatial summation in the central field.[12,13]

As both inferior and superior hemiretinal data derived from the GCC and RNFL modes are most often affected by glaucoma in the early to moderate stage of the disease,[2,24,28,29] it was important to study the pattern of the relationship in these areas in addition to the overall RNFLT. As illustrated in Figures 1 and 2, with both the global and the sectoral data, the relationship between function and structure was nonlinear on the standard dB-DLS scale. On the nonlogarithmic DLS scale, a nonlinear relationship was also apparent. Although direct comparison between studies can be misleading because of differences in patient populations, methods, and study design, the nonlinear relationship that we found between function (nonlogarithmic DLS) and structure identified in the present work differed from that reported by Leung et al.,[26] using TD OCT. However, our finding of a nonlinear structure–function relationship between dB-DLS, on the one hand, and both GCCT and pRNFLT data, on the other, agrees well with the reported relationships between dB-DLS and neuroretinal rim area.[30–33] Further support comes

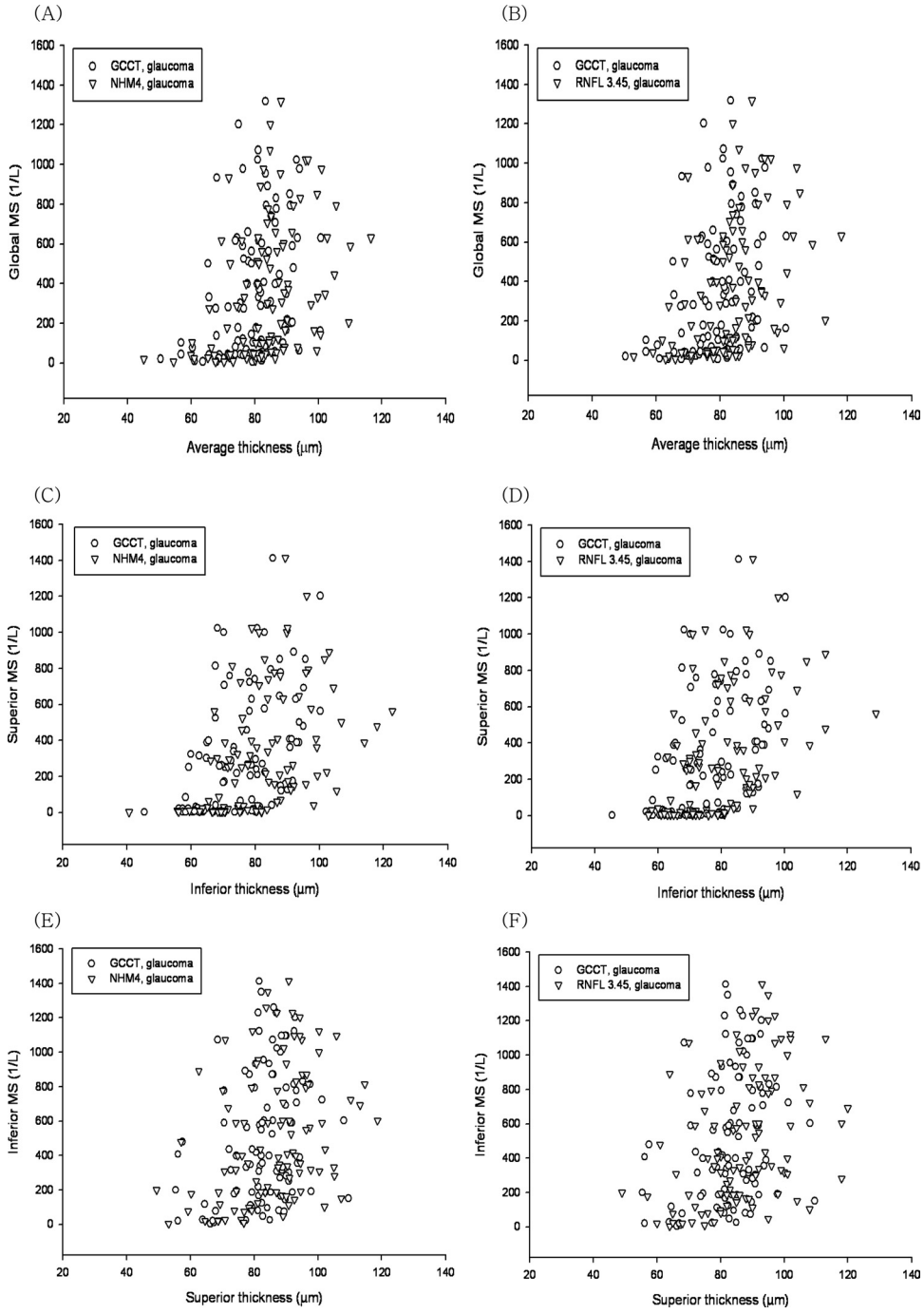

FIGURE 2. Scatter plots showing the associations between SD-OCT parameters and corresponding retinal sensitivities expressed on the 1/L scale. Average thicknesses versus global MS obtained in the (**A**) GCC and NMH4 and the (**B**) GCC and RNFL 3.45 modes. Inferior average thicknesses versus superior MS obtained in the (**C**) GCC and NHM4 and the (**D**) GCC and RNFL 3.45 modes. Superior average thicknesses versus inferior MS obtained in the (**E**) GCC and NMH4 and the (**F**) GCC and RNFL 3.45 modes.

from studies using SLP; this work correlated RNFL retardation data from glaucomatous patients with SAP retinal sensitivity.[10–12] The cited reports showed that the relationship between DLS and SLP is curvilinear on the dB scale and linear on the nonlogarithmic DLS scale.

There is no obvious explanation of the discrepancies between results of studies, including our present work, with respect to relationships expressed using the nonlogarithmic DLS scale. As pointed out by Leung et al.,[26] the relationship between the RNFLT and VF sensitivity may vary, not only with the methods of VF expression (dB versus nonlogarithmic 1/L), but also with the type of RNFL imaging device (Stratus OCT versus SD-OCT) used and the characteristics of the study subjects.

Although the nonlogarithmic DLS scale may be more appropriate for comparing structural and functional measurements than the standard dB scale, the latter scale may be more useful clinically, because the span of average thickness is smaller when GCCT data are used, and the strength of any association may thus appear to be less obvious when expressed in the nonlogarithmic DLS scale (Fig 2). Furthermore, the variability of perimetric measurements among subjects appears to be less when expressed on the dB-DLS scale than on the nonlogarithmic DLS scale. However, the use of a curvilinear model in association with the dB scale may lead to underestimation of the rate of change when thickness measurements are near normal, or patients are at an early stage of VF damage, thus giving the false impression that a functional reserve is present

Table 3. Comparison of the Linear and Logarithmic Models

	dB Scale		1/L Scale	
	Linear	Log	Linear	Log
GCC	606.1	595.1	1379.3	1368.7
GCC_sup	584.5	573.3	1408.6	1397.6
GCC_inf	665.5	654.4	1369.0	1359.1
RNFL1	599.7	587.7	1377.0	1366.3
RNFL1_sup	578.6	566.9	1405.5	1394.5
RNFL1_inf	661.2	647.9	1370.4	1359.3
RNFL2	600.5	588.5	1374.4	1363.4
RNFL2_sup	578.3	566.8	1401.2	1390.1
RNFL2_inf	664.8	651.7	1368.7	1357.3

The comparison was made by calculation of the AIC values in glaucomatous eyes ($n = 97$), between OCT thickness parameters and corresponding retinal sensitivity expressed on the dB and 1/L scales. Linear model, $y = a + bx$; logarithmic model, $y = a + b \log_{10} x$; inf, inferior hemiretina; sup, superior hemiretina.

and overestimates the rate of change in GCCT and pRNFLT in patients at more advanced stages of glaucomatous VF loss.

In our recent study,[34] evaluating the glaucoma discrimination ability of GCCT and pRNFLT measured by SD-OCT, GCCT showed a discrimination capacity comparable to that of pRNFLT in a group of glaucoma patients with early VF defects. When these results are combined with those of the present study, it is apparent that GCCT measurement by an SD-OCT device (RTVue-100; Optovue) may be as closely related to VF damage, as are pRNFL measurements. Thus, both GCC and pRNFL data offer similar diagnostic capability. Further longitudinal studies are needed to correlate GCC structural changes with its corresponding functional declines during the progression of glaucoma, using SD-OCT to validate the findings.

Our study included only eyes diagnosed with glaucoma based on abnormal perimetric results, without inclusion of patients showing structural damage alone. We enrolled only eyes with perimetric glaucoma on the assumption that, in eyes with normal SAP results, including preperimetric glaucomatous eyes or normal control eyes, little or no correlation between SAP sensitivity and RNFLT measurements would be evident. Further work is needed to validate this assumption.

Although the goal of our study was to illustrate and compare the extent of association between GCCT and pRNFLT measurements and MS in a given area using routine data from the SD-OCT printouts, the use of relatively large-area OCT data and corresponding VF analyses may not be optimal for evaluating the relationship between of GCCT and RNFLT with VF MS. Other limitations of the present study include the use of a relatively small sample size and that the sample was ethnically homogeneous (all were Asian). Data from a single ethnic group may not be generalized to other races. However, our study is exploratory in nature and is the first work evaluating structure–function relationships using the GCC mode of SD-OCT. The finding may be valuable in guiding further studies on the clinical utility of GCCT assessment employing SD-OCT.

In conclusion, GCCT and pRNFLT data obtained by SD-OCT (RTVue-100; Optovue) correlated significantly with retinal MS assessed by perimetry (HFA; Carl Zeiss Meditec, Inc.). The strength of structure–function relationships involving GCCT measurements compared well with those in which pRNFLT data were used. Regression models showed better fits when logarithmic equations were used, with VF sensitivity expressed in either nonlogarithmic 1/L units or on the standard dB scale.

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