

Differences in Relationship Between Macular Inner Retinal Layer Thickness and Retinal Sensitivity in Eyes With Early and Progressed Glaucoma

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PURPOSE. To determine if the relationship between retinal sensitivity and macular inner retinal layer thickness differs between primary open-angle glaucoma (POAG) with mild and advanced central visual field (VF) damage.

METHODS. One eye of 153 POAG patients was included. Using spectral-domain optical coherence tomography, we measured the average thickness of the macular ganglion cell-inner plexiform layers (GCIPLT) and the macular nerve fiber layer/GCIPL (ganglion cell complex [GCCT]) in a 0.9-mm-diameter ganglion cell displacement-adjusted circular area corresponding to the four central test points of the Humphrey Perimeter 24-2 program and correlated the results with the average retinal sensitivity (1/Lambert) at the corresponding test points, with adjustment for other confounding factors.

RESULTS. Ninety-three eyes had mild central and 60 eyes advanced central VF damage with an average total deviation (TD) of the four test points of greater than or equal to -4 decibels (dB) (mild group) and less than -4 dB (more severe group), respectively; the average mean deviations were -3.0 and -9.8 dB, respectively. In the mild group, the GCCT and GCIPLT were correlated significantly and positively with the average retinal sensitivity with partial regression coefficient of 0.007 and 0.005, respectively, and in the more severe group with partial regression coefficient of $0.019 = 0.007 + 0.012$ ($P = 0.007$) and $0.010 = 0.005 + 0.005$ ($P = 0.078$), respectively. The axial length and disc size were correlated with GCIPLT with marginal significance ($P = 0.052$ and $P = 0.042$).

CONCLUSIONS. The relationship between the macular GCC and GCIPL thickness and retinal sensitivity at the corresponding retinal areas differed between POAG with mild and advanced central VF damage.

Keywords: ganglion cell complex, macula, retinal sensitivity

Glaucoma damages the retinal ganglion cell (RGC) bodies and axons and is associated with characteristic patterns of visual field (VF) defects and changes in the appearance of the optic nerve head (ONH). Thinning of the RGC-related retinal layers caused by RGC loss is associated with decreased VF sensitivity. Structural and functional tests are indispensable for assessing the extent of glaucomatous damage, especially in early glaucoma.¹

A number of studies have used optical coherence tomography (OCT) to study correlations between standard automated perimetry (SAP)-determined sensitivity and OCT-determined thicknesses of the RGC-related retinal layers such as the circumpapillary retinal nerve fiber layer (cpRNFL); combined macular RNFL (mRNFL), ganglion cell layer (GCL) and inner plexiform layer (IPL), macular ganglion cell complex (GCC); and the combined macular GCL and IPL (GCIPL).²⁻¹⁴ Previous studies have agreed that the correlation between the OCT-

measured thicknesses of the RGC-related retinal layers and corresponding SAP sensitivities is weak and insignificant when the SAP sensitivities are normal.²⁻¹³ This finding has been explained by the fact that substantial RGC loss (i.e., at least 10% to approximately 20%) resulting from glaucomatous damage is needed to lower the measured SAP sensitivity to outside the normal range,^{2,3,15} and it is reasonable to assume that the SAP sensitivities on the linear scale (1/Lambert = $10^{\text{dB value}/10}$) or the decibel (dB) scale decrease linearly with decreases in the thicknesses of the RGC-related retinal layers or the density of the RGCs on the dB scale, respectively, once the RGC loss exceeds the critical point. In studying the relationship between the SAP sensitivities and thicknesses of the RGC-related retinal layers in the corresponding retinal areas, the GCC or GCIPL thickness in the macular region where most RGCs are located is advantageous over adopting the cpRNFL thickness, as the axons comprising the cpRNFL originate from different retinal



regions, and interindividual variation is believed to exist between the VF regions and the disc sectors.¹⁶⁻¹⁹

We recently reported that the GCC or GCIPL thickness corresponding to the central four test points of the Humphrey Field Analyzer (HFA) 24-2 program (Carl Zeiss Meditec, Dublin, CA, USA) was correlated significantly and positively with the corresponding linear scale SAP sensitivity at the four test points in normal eyes,¹⁴ although the slope of the regression line was much flatter than those reported in glaucomatous eyes.^{2,4-13} This finding suggested that the stage of glaucoma may also affect the relationship between the SAP sensitivities and thicknesses of the RGC-related layers in the corresponding retinal areas. In fact, Ajtony et al.⁵ reported that correlation between cpRNFL thickness and mean deviation (MD) value given by HFA 30-2 program in primary open-angle glaucoma (POAG) eyes fit a curvilinear regression model rather than a linear regression model. To the best of the authors' knowledge, however, it has not been studied whether correlation between SAP sensitivities and GCC or GCIPL thickness in the corresponding retinal area depends on the disease stage or not.

In the current study, we investigated if there is a difference in the slope characterizing the GCC or GCIPL thickness and the linear scale SAP sensitivity relationship in the macular region between POAG eyes with mild central VF damage and those with those advanced VF damage, after adjusting for the possible effect of age, disc size, and axial length.²⁰⁻²⁵

MATERIALS AND METHODS

Subjects

Patients with POAG were recruited using identical inclusion criteria at the four participating institutes (University of Tokyo, Kanazawa University, Kyoto University, and Tajimi Municipal Hospital). The institutional review board of each institution approved the study protocol and adhered to the tenets of the Declaration of Helsinki. Each subject provided written informed consent after obtaining an explanation of the study protocol. Patients fulfilling the inclusion criteria who were seen at one of the four institutions and agreed to participate in the study were consecutively enrolled and underwent the following ocular measurements: refraction and corneal curvature radius with an automatic refractometer (ARK-900; Nidek, Tokyo, Japan), best-corrected visual acuity, axial length with the IOLMaster (Carl Zeiss Meditec), and IOP by Goldmann applanation tonometry, and the following examinations: slit-lamp, dilated funduscopy, and testing with the HFA 24-2 Swedish Interactive Threshold Algorithm Standard (SITA-S) program (Carl Zeiss Meditec). Patients were included if they were accustomed to VF testing using an HFA that provided reliable and reproducible VF test results (fixation loss, false-positives, or false-negatives <20%) and had apparent glaucomatous changes in the ONH and/or apparent RNFL defects confirmed by the panel of glaucoma specialists (MA, MH, and AD) on stereo-fundus photographs and digitally constructed red-free photographs. The ONH changes included an apparent rim notch in the superior or inferior portion with a width of 0.1 or less disc diameter and a vertical cup-to-disc ratio over 0.7 in one eye that was greater than that of the fellow eye by a factor of 0.2 or more. The presence of glaucomatous VF defects was not a concern when apparent ONH findings and/or RNFL defects with a width greater than the major retinal vessel diameter at the disc margin were observed.

Other inclusion criteria included eyes with a refractive error of -6.0 diopters (D) or higher and less than 3.0 D; and the absence of a clinically relevant cataract or a history of other ocular pathologic changes that could affect the results of HFA

or OCT examinations, including incisional intraocular or refractive surgeries. The VF was checked using the HFA 24-2 SITA-S program within 3 months of the OCT examination and confirmed to reproduce the VFDs found in the previous tests. Glaucomatous VFDs were defined according to the criteria of Anderson and Patella.²⁶ Eyes with POAG were grouped based on the mild (mild group) or advanced central VF damage (more severe group) according to the extent of damage at the four central test points of the HFA 24-2 program. If both eyes of a participant fulfilled the inclusion criteria, the eye with better spectral-domain (SD)-OCT image quality was enrolled.

Optical Coherence Tomography Measurement

Optical coherence tomography scanning was performed using an SD-OCT1000 instrument (Topcon, Tokyo, Japan) equipped with a nonmydriatic fundus camera function. Data sets were obtained using the raster-scan protocol, where data were obtained from a $6.0 \times 6.0\text{-mm}^2$ area (512×128 pixels) centered on the fixation point over a period of approximately 2.5 seconds. To obtain accurately sized fundus images, the magnification was corrected according to the formula provided by the manufacturer based on the refractive error, corneal radius, and axial length. The correspondence of the fundus photographs and OCT images was confirmed automatically using an OCT projection image and localization of the major retinal vessels.

The data obtained during eye movements were discarded and the examination repeated. Images that were affected by involuntary blinking or saccades, indicated by breaks, shifting of the vessels, or the presence of a straight line across the fundus OCT image, or those with a quality factor less than 60% also were excluded. In the macular area, the fovea was identified automatically in the OCT image as the pixel with the thinnest total retinal thickness adjacent to the fixation point. The mRNFL and GCIPL were segmented automatically in all B-scan images.²⁷ An experienced examiner (AT) confirmed the image segmentation. Data for the GCC were obtained with the following formula: (mRNFL + GCIPL).

Immediately after the SD-OCT measurement, a color fundus photograph centered on the disc was taken with the nonmydriatic fundus camera function of the SD-OCT device. The disc area in the fundus photographs was identified by determining the area inside a closed spline curve fitted to seven manually determined points on the disc margin. The magnification was corrected as described previously.²⁰

Relationship Between GCC and GCIPL Thickness and the Linear Scale VF Sensitivity in Corresponding Retinal Areas

The GCC and GCIPL thicknesses (GCCT and GCIPLT) in a circular retinal area with a 0.9-mm diameter ($\sim 3^\circ$ of visual angle) corresponding to the four central test points of the HFA 24-2 program, adjusted for RGC displacement, were assessed in the SD-OCT raster-scan data. Ganglion cell displacement was estimated with the following formula: $y = 1.29 \times (x + 0.46)^{0.67}$, where y indicates ganglion cell eccentricity and x indicates cone eccentricity.²⁸ The dB values for the SAP sensitivity in the four central test points of the HFA 24-2 test program were anti-logged to obtain the sensitivity in the linear scale ($1/\text{Lambert} = 10^{0.1 \times \text{dB value}}$),^{2-4,6,8,11,29} of which the mean of the four central test points was calculated using the above four anti-logged dB values (LSAP_{4 test points}). Age,^{20-23,24,25} axial length or refraction,^{21,23,25} and disc size²⁰ are external factors that reportedly can affect the OCT-measured thicknesses of the cpRNFL, GCC, or GCIPL. The laterality and gender were excluded from the external factors according to the result of

TABLE 1. Characteristics of Eyes With Mild Central Visual Field Damage (Mild Group)

Age, y	58.3 ± 9.7
Men:women	33:60
Right:left eyes	48:45
Spherical equivalent refraction, diopters	-1.5 ± 2.2
MD, dB	-3.0 ± 3.7
TD ₄ test points, dB	-0.8 ± 1.5
Mean sensitivity of the 4 central test points, 1/Lambert	1,625 ± 583
Disc area, mm ²	2.38 ± 0.57
GCIPL ₄ test points, μm	79.0 ± 9.2
GCC ₄ test points, μm	106.8 ± 12.3

TD₄ test points represents the mean of total deviation value at the four central test points of the HFA 24-2 program, and the GCIPL₄ test points (GCC₄ test points) represents the mean thickness of the retinal ganglion cell-inner plexiform layer (ganglion cell complex) in a 0.9-mm-diameter circular retinal area corresponding to the four central test points of the HFA 24-2 program after correcting for RGC displacement.

our previous study.¹⁴ The possible effect of these factors was considered by multiple linear regression analysis:

$$\begin{aligned} \text{GCCT}_4 \text{ test points (GCIPL}_4 \text{ test points)} \\ = A_1 \times \text{age} + A_2 \times \text{Axial length (mm)} + A_3 \times \text{disc size} \\ + A_4 \times \text{LSAP}_4 \text{ test points} + A_5 \times \text{GLA} \times \text{LSAP}_4 \text{ test points} + A_6 \\ + A_7 \times \text{GLA} + \text{error} \end{aligned} \quad (1)$$

where GCCT₄ test points (GCIPL₄ test points) indicates the mean of the measured GCC (GCIPL) thickness in the four retinal areas in the mild and more severe groups, and GLA indicates a category variable that adopts 0 in the mild group and 1 in the more severe group. The effects of age, axial length, and disc size on the relationship between the GCCT₄ test points (GCIPL₄ test points) and LSAP₄ test points were assumed to be independent of disease stage. When the partial regression coefficients A₄ and A₅ both differed significantly from 0, it was thought that the GCCT₄ test points (GCIPL₄ test points) changed along with the LSAP₄ test points decrease, but the slope characterizing the relationship between them differed significantly between the mild and more severe groups after correction of other confounding factors. The data were analyzed using SPSS software (21.0J for Windows; SPSS Japan Inc., Tokyo, Japan).

TABLE 2. Characteristics of Eyes With Advanced Central VF Damage (More Severe Group)

Age, y	59.4 ± 11.7
Men:women	22:38
Right:left eyes	33:27
Spherical equivalent refraction, diopters	-1.9 ± 2.0
MD, dB	-9.8 ± 6.4
TD ₄ test points, dB	-11.1 ± 5.7
Mean sensitivity of the 4 central test points, 1/Lambert	819 ± 395
Disc area, mm ²	2.40 ± 0.64
GCIPL ₄ test points, μm	70.8 ± 8.8
GCC ₄ test points, μm	90.7 ± 13.6

TD₄ test points represent the mean of total deviation value at the four central test points of the HFA 24-2 program, and GCIPL₄ test points (GCC₄ test points) represent the mean thickness of the retinal ganglion cell-inner plexiform layer (ganglion cell complex) in a 0.9-mm-diameter circular retinal area corresponding to the four central test points of the HFA 24-2 program, after correcting for RGC displacement.

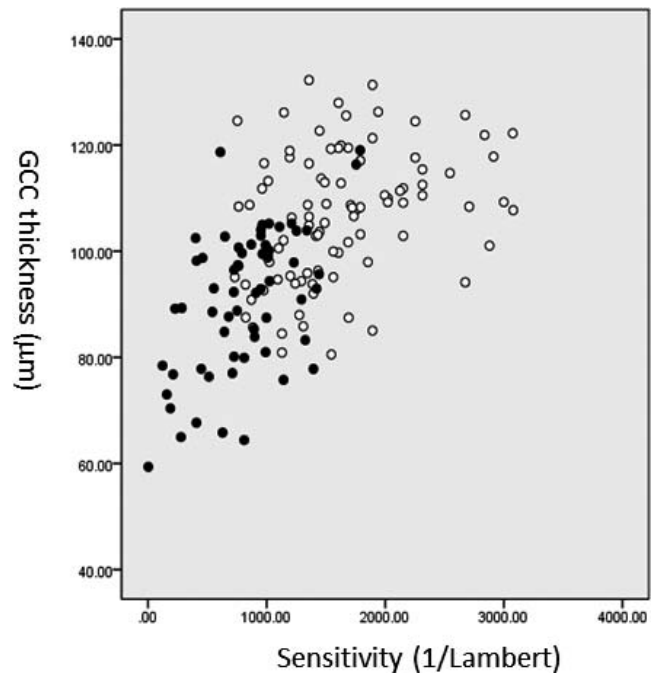


FIGURE 1. The mean thickness (μm) of the GCC layer in a 0.9-mm-diameter circular retinal area corresponding to each of the four central test points of the HFA 24-2 program after correcting for RGC displacement is plotted against the mean of the sensitivity at each of the four central test points on the linear scale (1/Lambert). The open circles indicate the results in the mild central VF damage group; the closed circles indicate those in the advanced central VF damage. A simple regression analysis without adjustment for other confounding factors yielded regression coefficient (slope) of 0.007 ± 0.002 ($P = 0.001$) in the former group and the difference in the regression coefficient between the former and latter groups was 0.011 ± 0.004 ($P = 0.011$) with the R^2 value of 0.399.

RESULTS

A total of 153 eyes of 153 patients with POAG who met the criteria were included and divided into those with mild central VF damage (mild group) and those with advanced central VF damage (more severe group). The mild group had the mean of the TDs at the four central test points of the HFA 24-2 program (TD₄ test points) of -4 dB or higher, and the more severe group had a TD₄ test points less than -4 dB. The mild group included 93 eyes of 93 patients whose age, MD, and TD₄ test points averaged 58.3 years, -3.0, and -0.8 dB, respectively (Table 1). The more severe group included 60 eyes of 60 patients whose age, MD, and TD₄ test points averaged 59.4 years, -9.8, and -11.1 dB, respectively (Table 2). A simple regression analysis between GCCT₄ test points (GCIPL₄ test points) (μm) and LSAP₄ test points (1/Lambert) without adjustment for other confounding factors yielded regression coefficient (slope) of 0.007 ± 0.002 (0.006 ± 0.001) ($P = 0.001$ [$P = 0.000$]) in the mild group and the difference in the regression coefficient between the mild and more severe groups was 0.011 ± 0.004 (0.005 ± 0.003) ($P = 0.011$ [$P = 0.128$]) with the R^2 value of 0.399 (0.296) (Figs. 1 and 2).

The results of the main multiple regression analysis are summarized in Tables 3 and 4. Multicollinearity among the explanatory variables was judged to be negligible. For the GCCT₄ test points (μm), the LSAP₄ test points (1/Lambert) were correlated significantly with partial regression coefficient of 0.007 ± 0.002 ($P = 0.002$). The difference in the partial regression coefficient for the LSAP₄ test points between the mild and more severe groups (A₅) was 0.012 ± 0.004 ($P = 0.008$).

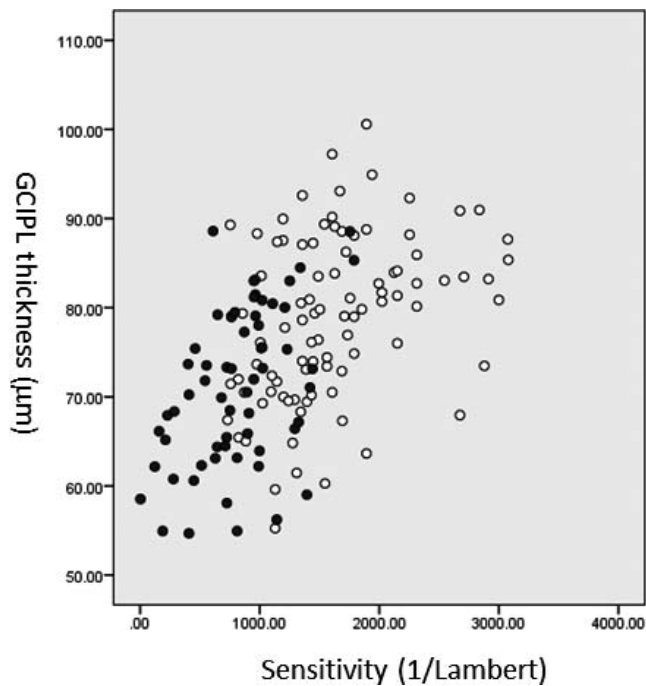


FIGURE 2. The mean thickness (μm) of GCIPL in a 0.9-mm-diameter circular retinal area corresponding to each of the four central test points of the HFA 24-2 program after correcting for RGC displacement is plotted against the mean of the sensitivity at each of the four central test points in the linear scale (1/Lambert). The *open circles* indicate the results in the mild central VF damage group; the *closed circles* indicate those in the advanced central VF damage group. A simple regression analysis without adjustment for other confounding factors yielded regression coefficient (slope) of 0.006 ± 0.001 ($P = 0.000$) in the former group and the difference in the regression coefficient between the former and latter groups was 0.005 ± 0.003 ($P = 0.128$) with the R^2 value of 0.296.

That is, when the GCCT_4 test points (μm) was plotted against the LSAP_4 test points (1/Lambert) after adjustment for other confounding factors, the slope (ΔGCCT_4 test points / ΔLSAP_4 test points) was approximately 2.7 times greater in the more severe than in the mild group ($0.019 = 0.007 + 0.012$ vs. 0.007). The R^2 value for the regression was 0.433.

TABLE 3. Results of Multiple Regression Analysis for the GCCT_4 test points, μm

Variable	Partial Regression Coefficient	P
Age, y	0.050 ± 0.107	0.645
Sensitivity,* 1/Lambert	0.007 ± 0.002	0.002
Sensitivity,† 1/Lambert	0.012 ± 0.004	0.008
Disc area, mm^2	-1.60 ± 1.69	0.347
Axial length, mm	-1.20 ± 0.83	0.151

The data are expressed as the mean \pm SE. GCCT_4 test points represent the mean thickness of the ganglion cell complex layer in a 0.9-mm-diameter circular retinal area corresponding to the four central test points of the HFA 24-2 program after correcting for RGC displacement.

* Partial regression coefficient for eyes with mild central VF damage (mild group).

† The difference in the partial regression coefficient between eyes with mild central VF damage (mild group) and those with advanced central VF damage (more severe group) corresponding to A_5 in Equation 1.

TABLE 4. Results of Multiple Regression Analysis for the GCIPL_4 test points, μm

Variable	Partial Regression Coefficient	P
Age, y	-0.048 ± 0.076	0.529
Sensitivity,* 1/Lambert	0.005 ± 0.002	0.005
Sensitivity,† 1/Lambert	0.005 ± 0.003	0.078
Disc area, mm^2	-2.45 ± 1.20	0.042
Axial length, mm	-1.18 ± 0.60	0.052

The data are expressed as the mean \pm SE. GCIPL_4 test points represent the mean thickness of the ganglion cell-inner plexiform layer in a 0.9-mm-diameter circular retinal area corresponding to the four central test points of the HFA 24-2 program after correcting for RGC displacement.

* Partial regression coefficient for eyes with mild central VF (mild group).

† The difference in the partial regression coefficient between eyes with mild central VF damage (mild group) and those with advanced central damage (more severe group) corresponding to A_5 in Equation 1.

For the GCIPL_4 test points (μm), the LSAP_4 test points (1/Lambert) was correlated significantly with partial regression coefficients of 0.005 ± 0.002 (SE) ($P = 0.005$) and the difference in the partial regression coefficient for the LSAP_4 test points between the early and progressed groups (A_5) was 0.005 ± 0.003 ($P = 0.078$). That is, when GCIPL_4 test points (μm) was plotted against the LSAP_4 test points (1/Lambert) after adjustment for other confounding factors, the slope (ΔGCIPL_4 test points / ΔLSAP_4 test points) tended to be approximately two times greater in the more advanced than in the mild group ($0.010 = 0.005 + 0.005$ vs. 0.005). Further, the axial length and disc size was negatively ($P = 0.052$ and $P = 0.043$) correlated with the GCIPL_4 test points, respectively. The R^2 value for regression was 0.347.

Supplementary analyses examined the relationship between the GCCT (GCIPLT) and LSAP at two test points in the upper (lower) hemifield or at each of the four central test points using the same equation. In these analyses, retinal areas with mild VF damage were defined as those with the mean or individual total deviation value (TD) of -4.0 dB or higher, and retinal areas with more severe VF damage as those with the mean or individual TD value less than -4.0 dB.

Hemifield-based analyses revealed the following results. At the retinal area corresponding to the two central test points in the upper hemifield, 90 eyes (90 cases) had mild central VF damage (mean TD ≥ -4 dB) and 63 eyes (63 cases) advanced central VF damage (mean TD < -4 dB). The LSAP was correlated significantly with the GCCT (GCIPLT) with a partial regression coefficient of 0.008 ± 0.003 (0.005 ± 0.002) ($P < 0.008$) and the difference in the partial regression coefficient between the both groups was 0.015 ± 0.006 (0.006 ± 0.0061), respectively ($P = 0.002$ and 0.133). At the retinal areas corresponding to the two central test points in the lower hemifield, 136 eyes (136 cases) had mild central VF damage (mean TD ≥ -4 dB) and 17 eyes (17 cases) advanced central VF damage (mean TD < -4 dB). The partial regression coefficient of the LSAP for the GCCT (GCIPLT) was 0.009 ± 0.002 (0.006 ± 0.002) ($P \leq 0.001$), whereas the differences in the partial regression coefficient between the both groups were 0.008 ± 0.011 (0.004 ± 0.009) ($P > 0.500$).

Pointwise analyses revealed the following results. At the retinal area corresponding to the superotemporal test point, the LSAP was correlated significantly with the GCCT (GCIPLT) with a partial regression coefficient of 0.012 ± 0.003 (0.008 ± 0.002) ($P < 0.001$) and the difference in the partial regression coefficient between the group with TD ≥ -4.0 dB ($n = 88$) and

that TD < -4.0 dB ($n = 65$) group was 0.050 ± 0.016 (0.032 ± 0.011) ($P < 0.006$). At the retinal areas corresponding to the inferior and superior nasal and inferior temporal test points, the numbers of eyes with TD ≥ -4.0 dB and those with TD < -4.0 dB were 121 to 143 and 10 to 32 of 153, respectively. The partial regression coefficient of the LSAP for the GCCT (GCIPLT) was 0.007 to approximately 0.009 ($0.005 \sim 0.007$) ($P < 0.002$), respectively, whereas the differences in the partial regression coefficient between the both groups were 0.009 to approximately 0.037 ($0.001 \sim 0.009$) ($P = 0.147 \sim 0.792$), respectively.

DISCUSSION

Greenfield et al.³⁰ first reported that the MD values were correlated significantly with the mean macular thickness measurements obtained using time-domain OCT in eyes with moderately advanced glaucoma. The GCIPL and GCC thicknesses also were reported to be correlated with the global or corresponding regional SAP sensitivity (in dB or the linear scale) in groups with only glaucomatous eyes or groups with glaucomatous and normal eyes.^{6-9,11} Although correlation between cpRNFL, GCC, or GCIPL thickness and retinal sensitivity was the subject of many previous studies, to the best of our knowledge, the current study is the first to report a significant difference in the relationship between the GCC (GCIPL) thickness and SAP linear scale sensitivity in corresponding macular regions between eyes with mild and advanced central VF. That is, ($\Delta GCCT_4$ test points [$\Delta GCIPLT_4$ test points]/ $\Delta LSAP_4$ test points) was approximately 2.7 (2.2) times greater, or given a same reduction in the retinal sensitivity, reduction in RGC-related inner retinal layer thickness will be approximately 2.5 times greater, in the macular area with advanced glaucomatous damage than in that with mild glaucomatous damage. Because many clinicians are focusing their attention to functional and structural test results obtained from the macular area of glaucoma eyes, we suppose that the current result would be clinically interesting. The higher significance ($P = 0.008$ vs. $P = 0.078$) for the intergroup difference in the GCCT/LSAP relationship than that in the GCIPLT/LSAP relationship is probably attributable to the fact that the GCCT included the macular RNFL thickness, in which a change parallels that in the GCIPLT. Using another SD-OCT instrument, Cho et al.⁶ plotted the average GCC thickness against the mean sensitivity over the entire HFA 24-2 test field in the linear scale in glaucomatous eyes with a mean MD of -7.0 dB. If the Δ average GCC thickness/ Δ mean sensitivity in the linear scale is approximated from the figure they presented, the value of approximately 0.025 is obtained, which is not far from that currently obtained for ($\Delta GCCT_4$ test points/ $\Delta LSAP_4$ test points) after adjustment for other confounding factors, 0.019, in the current POAG eyes with advanced central VF damage with a mean MD of -9.8 dB.

That finding also could be reproduced by the upper hemifield-based or pointwise analysis at the retinal area corresponding to the superotemporal test point from the central four test points. However, in the lower hemifield or at retinal areas corresponding to the other central four test points, the difference in $\Delta GCCT$ ($\Delta GCIPLT$)/ $\Delta LSAP$ between the eyes with mild and advanced central glaucomatous damage did not reach significance. In these cases, only 10 to 32 of the 153 eyes were classified into the group with advanced central glaucomatous damage, probably because the central four test points, especially those in the lower hemifield, are more likely to be spared until the very late stage of glaucoma. This small sample size in one arm may have substantially lowered the statistical power to detect an intergroup difference.

The difference between the current eyes with mild and advanced central glaucomatous damage may indicate that the relationship between GCCT (GCIPLT) or the number of RGCs and the perceived sensitivity at the corresponding retinal area is affected by the extent of the glaucomatous damage. Ajtony et al.⁵ reported that correlation between cpRNFL thickness and MD value in POAG eyes fit a curvilinear regression model rather than a linear regression model, which agrees with the current results obtained in the macular area. One possible explanation may be plasticity in the visual cortex or normal cerebral adaptation to chronic modifications in the visual input caused by slowly progressing glaucomatous damage.³¹

In the current mild group, the mean sensitivity of the central four test points in the dB scale averaged 32.1 dB, whereas it was 32.9 dB in normal eyes in our previous report.¹⁴ The corresponding GCCT₄ test points (GCIPLT₄ test points) in the mild group was 106.8 (79.0) μm , and that in the normal eyes¹⁴ calculated under the same conditions was 121.5 (90.3) μm . The intergroup difference in GCCT₄ test points (GCIPLT₄ test points), 14.7 (11.3) μm , was highly significant ($P < 0.001$) after adjustment for the intergroup differences in age, axial length, and SAP sensitivity, corresponding to approximately 35% of the dynamic range of the GCCT₄ test points (GCIPLT₄ test points) we approximated previously.¹⁴ This finding agreed with the previous finding that a substantial number of RGCs was lost before manifest VF damage developed.¹⁵ Further, it is obvious that the ($\Delta GCCT_4$ test points [$\Delta GCIPLT_4$ test points]/ $\Delta LSAP_4$ test points) value of the current mild group, 7 (5) $\mu\text{m}/1000$ (1/Lambert), cannot explain the above difference in the GCCT₄ test points (GCIPLT₄ test points), 14.7 (11.3) μm , and the difference in the LSAP₄ test points, ($2064 - 1625 \approx 440$ [1/Lambert]), which suggested that mild glaucomatous damage is associated not only with the reduced thickness of the RGC-related retinal layers (or number of RGCs), but also the change in the relationship between its thickness (or number of RGCs) and perceived visual sensitivity. Thus, it may not be adequate to analyze the difference between the normal eyes and those with mild glaucomatous damage using difference in the partial regression coefficient (slope) given by a same numerical formula. On the other hand, the difference in the GCCT₄ test points (GCIPLT₄ test points) between the mild and more severe groups, ($16.1 = 106.8 - 90.7$ [$8.2 = 79.0 - 70.8$] μm), and the LSAP₄ test points, ($809 = 1,625 - 816$ [1/Lambert]) seems to be compatible with the ($\Delta GCCT_4$ test points [$\Delta GCIPLT_4$ test points]/ $\Delta LSAP_4$ test points) value of the more severe group, 19 (11) $\mu\text{m}/1000$ (1/Lambert).

In normal eyes, the GCCT₄ test points (GCIPLT₄ test points) was correlated strongly with age,¹⁴ whereas age was not correlated significantly in the current eyes. The effect of glaucoma on the GCCT₄ test points (GCIPLT₄ test points) may be much stronger than that of physiologic aging in eyes with POAG. In POAG eyes, the GCIPLT₄ test points was negatively correlated with a partial regression coefficient of approximately 1.2 $\mu\text{m}/\text{mm}$ to axial length, which agreed with the value reported by Mwanza et al.²⁵ in normal eyes, approximately 1.0 $\mu\text{m}/\text{mm}$. These findings suggested that the effect of refraction must be corrected when studying the relationship between the RGC-related retinal layer thickness and SAP sensitivity in both normal and POAG eyes. Disc size also was negatively correlated only with the GCIPLT₄ test points in the current POAG eyes. Mwanza et al.²⁵ reported that the GCIPL was not correlated with disc size in normal eyes. Further, the relationship between the disc size and glaucomatous damage remains controversial.^{32,33} Thus, it seems difficult to discuss the pathophysiological relationship between the GCIPLT and disc size in POAG eyes based on the current results, and this issue deserves future study. The possibility of a cohort effect in this study may not be excluded.

The current study had several limitations, the first being its cross-sectional design. Disease stage-dependent differences, if they exist, should be investigated in a longitudinal study. Second, we could not include a large number of POAG eyes with very advanced regional damage, because it was difficult to recruit enough patients with a dense central scotoma who met the inclusion criteria. The structure/function relationship in very advanced POAG awaits future studies. Third, we assumed that there was a linear relationship between the GCCT₄ test points (GCIPLT₄ test points) and SAP sensitivity in the linear scale. However, the current results suggested that the value of $(\Delta\text{GCCT}_{4 \text{ test points}} / \Delta\text{GCIPLT}_{4 \text{ test points}}) / \Delta\text{LSAP}_{4 \text{ test points}}$ derived from current multiple linear regression analysis could reasonably explain the difference in GCCT₄ test points (GCIPLT₄ test points) and LSAP₄ test points between the mild and more severe POAG group. This result may indicate that the linear regression model was an acceptable approximation as far as the current subjects were concerned. Fourth, structure-function relationship in the macular area should be better studied adopting HFA 10-2 test results. What was reported in the current communication is the relationship at the most central four test points of HFA 24-2 test program. Future studies using HFA 10-2 test results should yield more information on the disease stage-dependent difference in the structure-function relationship in the macular area.

In summary, we found that the relationship between the GCC (GCIPL) thickness in retinal areas corresponding to the central four test points of the HFA 24-2 program and SAP sensitivity in the linear scale at these points differed between the eyes with mild central VF damage and those with advanced central VF damage from POAG. This finding suggested that not only the number or density of RGCs but also other local or central nervous system factors relating to perceived visual sensitivity may be modified along with progression of POAG from its early stage to the moderately advanced stage.

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References

- Johnson CA, Cioffi GA, Liebmann JR, Sample PA, Zangwill LM, Weinreb RN. The relationship between structural and functional alterations in glaucoma: a review. *Sem Ophthalmol*. 2000;15:221-233.
- Hood DC, Kardon RH. A framework for comparing structural and functional measures of glaucomatous damage. *Prog Retin Eye Res*. 2007;26:688-710.
- Harwerth RS, Wheat JL, Fredette MJ, Anerson DR. Linking structure and function in glaucoma. *Prog Retin Eye Res*. 2010; 29:249-271.
- Hood DC, Anderson SC, Wall M, Raza AS, Kardon RH. A test of linear model of glaucomatous structure-function loss reveals sources of variability in retinal nerve fiber and visual field measurements. *Invest Ophthalmol Vis Sci*. 2009;50:4254-4266.

- Ajtony C, Balla Z, Somoskeoy S, Kovacs B. Relationship between visual field sensitivity and retinal nerve fiber layer thickness as measured by optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2007;48:258-263.
- Cho JW, Sung KR, Lee S, et al. Relationship between visual field sensitivity and macular ganglion cell complex thickness as measured by spectral-domain optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2010;51:6401-6407.
- Kim NR, Lee ES, Seong GJ, Kim JH, An HG, Kim CY. Structure-function relationship and diagnostic value of macular ganglion cell complex measurement using Fourier-domain OCT in glaucoma. *Invest Ophthalmol Vis Sci*. 2010;51:4646-4651.
- Rao HL, Zangwill LM, Weinreb RN, Leite MT, Sample PA, Medeiros FA. Structure-function relationship in glaucoma using spectral-domain optical coherence tomography. *Arch Ophthalmol*. 2011;129:864-871.
- Raza AS, Cho J, de Moraes CGV, et al. Retinal ganglion cell layer thickness and local visual field sensitivity in glaucoma. *Arch Ophthalmol*. 2011;129:1529-1536.
- Wheat JL, Rangaswamy NV, Harwerth RS. Correlating RNFL thickness by OCT with perimetric sensitivity in glaucoma patients. *J Glaucoma*. 2012;21:95-101.
- Shin HY, Park HY, Jung KI, Park CK. Comparative study of macular ganglion cell-inner plexiform layer and peripapillary retinal nerve fiber layer measurement; structure-function analysis. *Invest Ophthalmol Vis Sci*. 2013;54:7344-7353.
- Wollstein G, Kagemann L, Bilonick RA, et al. Retinal nerve fibre layer and visual function loss in glaucoma: the tipping point. *Br J Ophthalmol*. 2012;96:47-52.
- Alasil T, Wang K, Yu F, et al. Correlation of retina nerve fiber layer thickness and visual fields in glaucoma: a broken stick model. *Am J Ophthalmol*. 2014;157:953-959.
- Araie M, Saito H, Tomidokoro A, Murata H, Iwase A. Relationship between macular inner retinal layer thickness and corresponding retinal sensitivity in normal eyes. *Invest Ophthalmol Vis Sci*. 2014;55:7199-7205.
- Quigley HA, Dunkelberger GR, Green GR. Retinal ganglion cell atrophy correlated with automated perimetry in human eyes with glaucoma. *Am J Ophthalmol*. 1989;107:453-464.
- Wirtschafter JD, Becker WL, Howe JB, Younge BR. Glaucoma visual field analysis by computed profile of nerve fiber function in optic disc sectors. *Ophthalmology*. 1982;89:255-267.
- Weber J, Dannheim F, Dannheim D. The topographical relationship between optic disc and visual field in glaucoma. *Acta Ophthalmol*. 1990;68:568-574.
- Garway-Heath DE, Poinoosawmy D, Fitzke FW, Hitchings RA. Mapping the visual field to the optic disc in normal tension glaucoma eyes. *Ophthalmology*. 2000;107:1809-1815.
- Ferreras A, Pablo LE, Garway-Heath DE, Fogagnolo P, García-Feijoo J. Mapping standard automated perimetry to the peripapillary retinal nerve fiber layer in glaucoma. *Invest Ophthalmol Vis Sci*. 2008;49:3018-3025.
- Hirasawa H, Tomidokoro A, Araie M, et al. Peripapillary retinal nerve fiber layer thickness determined by spectral-domain optical coherence tomography in ophthalmologically normal eyes. *Arch Ophthalmol*. 2010;128:1420-1426.
- Ooto S, Hangai M, Tomidokoro A, et al. Effects of age, sex, and axial length on the three-dimensional profile of normal macular layer structures. *Invest Ophthalmol Vis Sci*. 2011; 52:8769-8779.
- Girkin CA, McGwin G Jr, Sinai MJ, et al. Variation in optic nerve and macular structure with age and race with spectral-domain optical coherence tomography. *Ophthalmology*. 2011; 118:2403-2408.
- Knight OJ, Girkin CA, Budenz DL, Durbin MK, Feuer WJ, Cirrus OCT Normative Database Study Group. Effect of race, age, and axial length on optic nerve head parameters and

- retinal nerve fiber layer thickness measured by Cirrus HD-OCT. *Arch Ophthalmol*. 2012;130:312-318.
24. Ooto S, Hangai M, Sakamoto A, et al. Three-dimensional profile of macular retinal thickness in normal Japanese eyes. *Invest Ophthalmol Vis Sci*. 2010;51:465-467.
 25. Mwanza JC, Durbin MK, Budenz DL, et al. Cirrus OCT Normative Database Study Group. Profile and predictors of normal ganglion cell-inner plexiform layer thickness measured with frequency-domain optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2011;52:7872-7879.
 26. Anderson DR, Patella VM. *Automated Static Perimetry*. St. Louis: Mosby, Inc.; 1999:152-153.
 27. Yang Q, Reisman CA, Wang Z, et al. Automated layer segmentation of macular OCT images using dual-scale gradient information. *Opt Express*. 2010;18:21293-21307.
 28. Sjöstrand J, Popovic Z, Conradi N, Marshall J. Morphometric study of the displacement of retinal ganglion cells subserving cones within the human fovea. *Graefes Arch Clin Exp Ophthalmol*. 1999;37:1014-1023.
 29. Swanson WH, Felius J, Pan F. Perimetric defects and ganglion cell damage: interpreting linear relations using a two-stage neural model. *Invest Ophthalmol Vis Sci*. 2004;45:466-472.
 30. Greenfield DS, Bagga H, Knighton RW. Macular thickness changes in glaucomatous optic neuropathy detected using optical coherence tomography. *Arch Ophthalmol*. 2003;121:41-46.
 31. Safran AB, Landis T. From cortical plasticity and unawareness of visual field defects. *J Neuroophthalmol*. 1999;19:84-88.
 32. Quigley HA, Varma R, Tielsch JM, Katz J, Sommer A, Gilbert DL. The relationship between optic disc area and open-angle glaucoma: the Baltimore Eye Surgery. *J Glaucoma*. 1999;8:347-352.
 33. Wang L, Damji KF, Munger R, et al. Increased disc size in glaucomatous eyes vs normal eyes in the Reykjavik eye study. *Am J Ophthalmol*. 2003;135:226-228.