Structure–Function Relationship in Glaucoma Using Ganglion Cell–Inner Plexiform Layer Thickness Measurements

Harsha L. Rao, Muhammad Qasim, Raza S. M. Hussain, Manideepak Januwada, Lalitha N. Pillutla, Viquar U. Begum, Aditya Chaitanya, Sirisha Senthil, and Chandra S. Garudadri

VST Glaucoma Center, L V Prasad Eye Institute, Banjara Hills, Hyderabad, India

Correspondence: Harsha L. Rao, Kallam Anji Reddy Campus, L V Prasad Eye Institute, Banjara Hills, Hyderabad 500034, India; harshalaxmanarao@gmail.com.

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Purpose. To evaluate the structure–function relationship between ganglion cell–inner plexiform layer (GCIPL) thickness at the macula and 10-2 standard automated perimetry (SAP) in glaucoma and to evaluate the relationship using a recently proposed linear model.

Methods. In a cross-sectional analysis, structure–function relationship was determined in 50 glaucomatous eyes (40 patients, mean deviation: −15.4 ± 7.5 dB) and 21 control eyes (13 subjects, mean deviation: −3.4 ± 3.0 dB), which had undergone 10-2 SAP and GCIPL imaging on the same day. Functional loss was derived from total deviation numerical values on 10-2 SAP and calculated on both a linear (reciprocal of Lambert) and a decibel scale after accounting for the retinal ganglion cell displacement at the macula. Strength of relationship was reported as coefficient of determination (R^2) of the linear regression models fitted to the data separately for different sectors. The relationship was also evaluated using a linear model.

Results. The R^2 for the associations between GCIPL thickness sectors and the corresponding sector SAP total deviation values ranged from 0.19 (for superonasal GCIPL sector) to 0.60 (for average GCIPL thickness) when functional loss was calculated on the decibel scale and 0.16 (for superonasal sector) to 0.54 (for inferior sector) on the linear scale. All associations were statistically significant ($P < 0.05$). The linear model fitted the data reasonably well.

Conclusions. Significant structure–function associations were found between GCIPL thickness measurements at the macula and the functional loss measured on 10-2 SAP in glaucoma. Best fit was found for the inferior and average GCIPL sector thickness. The linear model was useful to study the structure–function relationship.

Keywords: glaucoma, structure–function relationship, ganglion cell–inner plexiform layer, visual field

Glaucoma is traditionally defined as a chronic, progressive optic neuropathy with characteristic optic nerve head (ONH) and retinal nerve fiber layer (RNFL) changes. However, with the advent of spectral-domain optical coherence tomography (SDOCT), another region that has been shown to demonstrate structural changes in glaucoma is the macula. Imaging the inner retinal layers at the macula has evolved as a useful modality to diagnose glaucoma.[1–9] Standard automated perimetry (SAP) has been the preferred method to evaluate the corresponding functional loss in glaucoma.

Multiple studies have evaluated the structure–function relationship in glaucoma using different measurement methods of ONH and RNFL and have shown that the relationship is modest at best.[10–18] One of the reasons for this imperfect relationship is the inability to conduct precise local measurements to compare structure with corresponding retinal areas of function because for a given region of the retina, the axons in the RNFL are originating from different regions.[19] Studies evaluating the structure–function relationship in glaucoma at the macula are limited. Earlier studies with SDOCT used the RNFL thickness at the papillomacular bundle to correlate with macular function.[18,20,21] However, the RNFL of the temporal region has been shown to demonstrate a high degree of variability, even in healthy individuals.[22] Multiple studies subsequently evaluated the structure–function relationship at the macula using the inner retinal layer thickness at the macula obtained with SDOCT.[20,23–25] Inner retinal layer thickness at the macula generally included the RNFL, ganglion cell layer, and the inner plexiform layer thickness (together called the ganglion cell complex, GCC). Measuring specifically the ganglion cell and inner plexiform layer (GCIPL) thickness at the macula is expected to improve the structure–function relationship in glaucoma, and a few recent studies have evaluated this.[19,26–29] The other issue to note is that most of the previous studies used the 24-2 program of SAP to evaluate the functional changes at the macula.[20,23–27,29] However, the 24-2 program estimates retinal sensitivity at the macula using only 16 points, each of which is 6° apart. The sampling density of the 24-2 program to estimate visual sensitivity at the macula may therefore be inadequate. Also the locations of the ganglion cells stimulated by the central 24-2 visual field (VF) test points are farther from the fovea because the ganglion cells in the fovea are displaced.[30,31]

The purpose of our study was to evaluate the structure–function relationship at the macula using the GCIPL thickness measurements of SDOCT and the 10-2 program of SAP. The 10-2 program of SAP samples the retinal sensitivity at the macula better by using 68 points, each of which is 2° apart. The other

purpose of our study was to evaluate this relationship using the model proposed by Hood and Kardon.[22]

Methods

Subjects for the current analysis were recruited from two ongoing prospective studies. One was the Longitudinal Glaucoma Evaluation Study (LOGES), a prospective longitudinal study conducted at the L V Prasad Eye Institute, Hyderabad, India, to evaluate the structure and function in glaucoma longitudinally. The study methodology of LOGES has been described previously.[9] The other was a cross-sectional study to evaluate the structure–function relationship using microperimetry, SAP, and SDOCT in glaucoma. Written informed consent was obtained from all participants, and the Ethics Committee of L V Prasad Eye Institute approved both the study methodologies. All methods adhered to the tenets of the Declaration of Helsinki for research involving human subjects.

Inclusion criteria for the current study were age $\geq$ 18 years, best-corrected visual acuity of 20/40 or better, and refractive error within $\pm$5 diopter (D) sphere and $\pm$3D cylinder. Exclusion criteria were presence of any media opacities that affected SDOCT scans and SAP results, and any retinal (including macular) or neurological disease other than glaucoma that could confound the evaluations. All participants underwent a comprehensive ocular examination, which included a detailed medical history, best-corrected visual acuity measurement, slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, dilated fundus examination, VF examination with SAP, and SDOCT imaging with Cirrus HD-OCT (Carl Zeiss Meditec, Inc., Dublin, CA, USA).

Spectral-domain OCT examination was performed with Cirrus HD-OCT (software version 6.0). The protocol used for this study was Macular Cube 200×200 for the GCIPL thickness measurements. This protocol has been explained in detail previously.[26,32] Ganglion cell analysis (GCA) is software that measures the GCIPL thickness within a 14.13-mm^2 elliptical annulus centered on the fovea with an inner vertical radius of 0.5 mm and outer vertical radius of 2 mm, stretched horizontally by 20%. The thickness parameters derived from GCA are the average GCIPL thickness across the entire elliptical annulus and the thickness at six 60° sectors of the elliptical annulus.

The visual field examination was performed using a Humphrey Field analyzer, model 750i (Zeiss Humphrey Systems, Dublin, CA, USA), with the Swedish interactive threshold algorithm (SITA) standard 10-2 program. Visual fields were considered reliable if the fixation losses were less than 20% and false-positive and -negative response rates were less than 15%. The correspondence map for structure–function evaluation at the macula using the GCIPL sectors of Cirrus HD-OCT has been described previously.[33] This map also considered the displacement of the RGCs at the macula by using equations derived from histological analysis to approximate the location of the RGCs with each SAP test point.[30] Standard automated perimetry–measured visual sensitivity loss was calculated by first converting the decibel (dB) scale values at each test location on the total deviation numerical plot to a linear scale (reciprocal of Lambert scale) using the following formula:

$$\frac{1}{\text{Lambert}} = (10)^{0.1*dB}. \quad (1)$$

Then values from all test points within the visual field sectors corresponding to the anatomic sectors described above were averaged. The average visual sensitivity loss per sector was converted back to dB scale for the analysis.

Control eyes had nonglaucomatous optic discs as assessed by experts on clinical examination and normal VF. Perimetric glaucoma eyes had glaucomatous optic discs (neuroretinal rim thinning, notching or localized or diffuse RNFL defects) and glaucomatous VF results. Visual fields were classified as glaucomatous on the SITA standard 24-2 program if the pattern standard deviation had a P value less than 5% and the glaucoma hemifield test result was outside normal limits.[34] Visual fields were classified as normal otherwise. All glaucomatous eyes had VF defects involving one or more of the central four points of the 24-2 field and had 10-2 VF performed to evaluate the central VF defect in greater detail. The VF examination and the HD-OCT examination were done on the same day in all the subjects.

Statistical Analysis

Descriptive statistics included mean and standard deviation for all continuous variables. Structure–function associations were investigated by using linear ($y = ax + b$) regression between GCIPL thickness and visual sensitivity loss expressed in both linear and dB scale. The associations are reported as the coefficient of determination (R^2) of the linear regression models. Locally weighted scatterplot smoothing (lowess) curves were also used to fit the relationship graphically. Lowess is a modeling method that combines the linear least square regression with the nonlinear regression.[35] It does this by fitting simple models to localized subsets of the data to build up a function that describes the deterministic part of the variation in the data, point by point. Lowess curve has an advantage in describing the structure–function relationship because it does not require the specification of a function (e.g., linear, quadratic) to fit a model to all of the data in a given sample.

Details of the linear model proposed by Hood and Kardon are explained elsewhere.[19,22] This model makes some basic assumptions to evaluate the structure–function relationship. It proposes that the thickness of a structure (GCIPL here), R, measured with OCT is made up of two components, thickness due to retinal ganglion cell bodies and dendrites, called signal or s_o, and the residual thickness due to glial cells and blood vessels, called base level or b, so that the measured GCIPL thickness is given by the equation

$$R = s_o + b. \quad (2)$$

It also proposes that visual sensitivity decreases as the signal s_o decreases, but the residual b does not change. So the above equation is written as

$$R = s_o{}^*10^{0.1*D} + b, \quad (3)$$

where D is the loss of visual sensitivity on the dB scale, represented on the total deviation numeric map. Base level or b is taken as the GCIPL thickness corresponding to a decrease in the visual sensitivity of more than 15 dB (compared to age-matched normal) on the total deviation numeric plot.[19]

Converting the visual sensitivity loss to linear scale, the above equation can be represented as

$$R = s_o{}^*T + b, \quad (4)$$

where T is the visual sensitivity loss on a linear scale.

Statistical analyses were performed using commercial software (Stata ver. 12.0; StataCorp, College Station, TX, USA). A P value of 0.05 was considered statistically significant.

Results

Ninety eyes of 65 participants were evaluated for inclusion into the study. Eight eyes of 6 subjects with unreliable 10-2 VFs and

Table 1. Structural and Functional Characteristics of the Participants

	Control Group, 21 Eyes of 13 Subjects	Glaucoma Group, 50 Eyes of 40 Subjects	*P* Value
Age, y	45.5 ± 11.9	52.3 ± 11.4	0.07
Visual field parameters			
Mean deviation, dB	−3.4 ± 3.0	−15.4 ± 7.5	<0.001
Pattern standard deviation, dB	1.7 ± 1.2	10.6 ± 3.7	<0.001
GCIPL parameters, μm			
Superotemporal	76.9 ± 5.3	59.1 ± 10.2	<0.001
Superior	78.1 ± 7.1	63.1 ± 11.0	0.001
Superonasal	81.2 ± 6.1	68.9 ± 11.6	<0.001
Inferonasal	80.4 ± 4.6	63.9 ± 11.1	<0.001
Inferior	77.9 ± 4.9	56.6 ± 7.8	<0.001
Inferotemporal	78.0 ± 5.7	53.3 ± 8.5	<0.001
Average	78.8 ± 5.1	60.8 ± 8.2	<0.001

All values are represented as mean ± standard deviation.

11 eyes of 6 subjects with either signal strength on HD-OCT of less than 6 and/or segmentation error were excluded, and 71 eyes of 53 subjects were included for the final analysis. Of these, 21 were control eyes (13 subjects) and 50 were glaucomatous (40 subjects). On 24-2 SAP, 8 of the glaucomatous eyes had a mean deviation (MD) better than −6 dB, 14 had a MD between −6 and −12 dB, and 28 had a MD worse than −12 dB. On 10-2 SAP, 29 of the glaucomatous eyes had a MD better than −15 dB and 21 had a MD worse than −15 dB. Table 1 shows the characteristic features of the control and the glaucomatous eyes.

Table 2 shows the R^2 values of the linear regression models evaluating the structure–function relationships between GCIPL thickness measurements (expressed in linear scale) and visual sensitivity loss expressed in dB and linear scales. The strongest R^2 values were found with the average inferior and inferotemporal sector GCIPL thickness measurements. The R^2 values varied according to the severity of VF loss. The R^2 for association between structure and function was not statistically significant ($P > 0.05$) with any GCIPL parameter in normal subjects and in glaucomatous eyes with MD worse than −15 dB on 10-2 VF. The R^2 value was statistically significant ($P < 0.05$) with most GCIPL parameters in glaucomatous eyes with MD better than −15 dB. In glaucomatous eyes with MD better than −15 dB, R^2 values ranged between 0.04 (for inferonasal GCIPL thickness) and 0.46 (for superior GCIPL thickness) when visual sensitivity loss was represented in dB scale. The R^2 values ranged between 0.06 (for inferonasal GCIPL thickness) and 0.51 (for inferior GCIPL thickness) when visual sensitivity loss was represented in linear scale.

Figures 1 and 2 show the model proposed by Hood and Kardon[22] fit to the GCIPL sectors in our data. The base level *b* was calculated as the GCIPL thickness corresponding to a mean loss of sensitivity of 15 dB or lower in each sector. The mean value of *b* ranged between 49.0 μm (in the inferotemporal GCIPL sector) and 60.0 μm (in the superonasal GCIPL sector). The dashed lines in the figures were derived by joining the mean GCIPL thickness in a particular sector in normal subjects with base level *b* in the sector, according to the method proposed by Hood and Kardon.[22] Figures 1 and 2 show the model with the visual sensitivity loss in dB and in linear scale, respectively. Solid lines in the figures represent the lowess curves fit to the actual data. The simple linear model fitted our data reasonably well. Compared with the lowess curves, the predicted curves seemed to overestimate structural damage in eyes with moderate VF loss (visual sensitivity loss between −5 and −15 dB).

Discussion

In this study to evaluate the structure–function relationship between the GCIPL thickness and visual sensitivity loss measured from 10-2 VFs, we found strong linear relationships with average and inferior sector GCIPL thickness measurements. Studies evaluating the structure–function relationship using the GCIPL thickness and visual sensitivities of 10-2 VF are sparse.[19,28] Raza et al.[19] evaluated the structure–function relationship using GCIPL thickness in a small sample of 19 control and 14 glaucoma subjects. Spectral-domain OCT used in the study was from a different manufacturer (3D-OCT 1000; Topcon, Inc., Paramus, NJ, USA), and the GCIPL sectors consisted of five concentric ring sectors with radius ranging from 3.4° to 9.7° from the fovea. The authors found that the correlation coefficients were higher (0.71–0.74) within the

Table 2. Structure–Function Relationships With Ganglion Cell–Inner Plexiform Layer (GCIPL) Thickness Measurements

	Loss of Visual Sensitivity in Corresponding Sector, Decibel Scale		Loss of Visual Sensitivity in Corresponding Sector, Linear Scale	
GCIPL Sector	R^2	*P* Value	R^2	*P* Value
Superotemporal	0.26	<0.001	0.21	<0.001
Superior	0.27	<0.001	0.26	<0.001
Superonasal	0.19	0.001	0.16	<0.001
Inferonasal	0.21	<0.001	0.24	<0.001
Inferior	0.47	<0.001	0.54	<0.001
Inferotemporal	0.31	<0.001	0.35	<0.001
Average	0.60	<0.001	0.43	<0.001

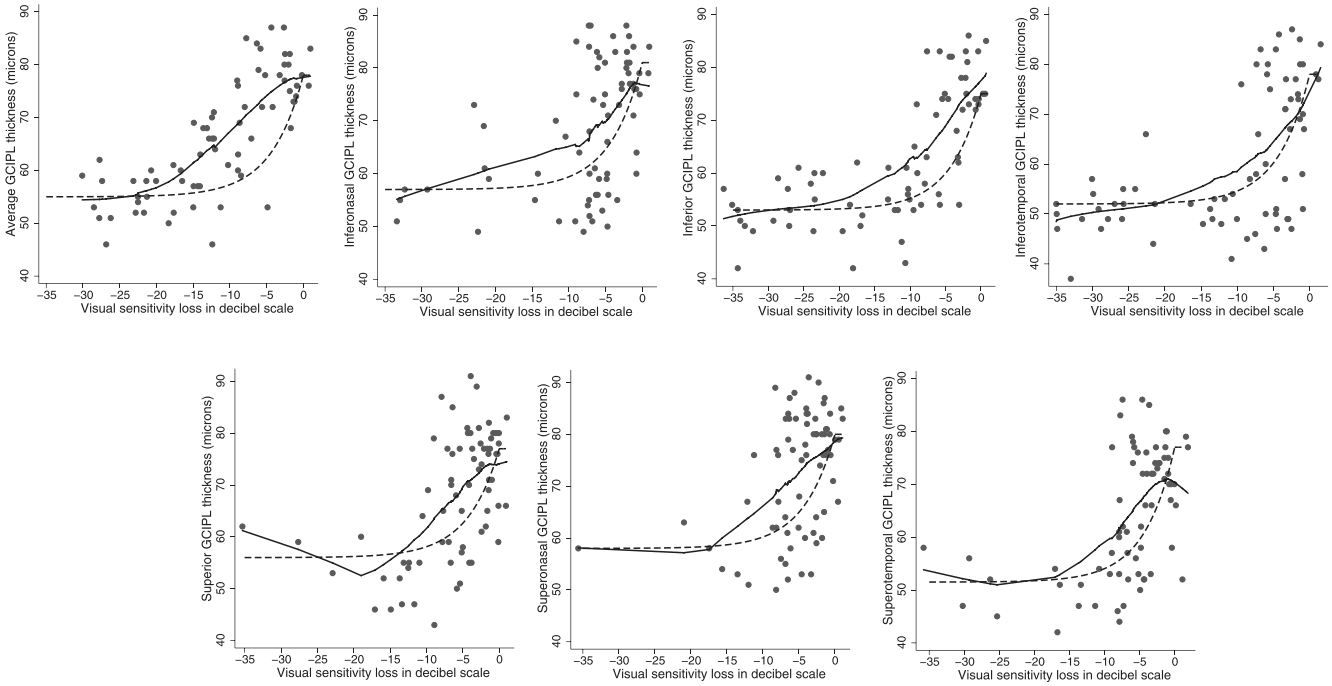

Figure 1. Linear model showing the relationship between ganglion cell–inner plexiform layer (GCIPL) thickness parameters and corresponding sector visual sensitivity loss in decibel (dB) scale. *Solid black line* represents the lowess curve fitting our data. *Dashed line* represents the simple linear model fit to the data.

central 7.2° compared to beyond this region (0.53–0.65).[19] Another study by Ohkubo et al.[28] also used 3D-OCT for GCIPL thickness measurements and correlated the GCIPL thickness with the visual sensitivity of all 68 points of 10-2 VF separately. They found the correlation coefficients in the central 5.8° to range between 0.36 and 0.72.[28] These results, however, cannot be directly compared to those of our study as the GCIPL sectors were not comparable between the studies.

The GCIPL sectors showing the strongest linear associations with visual sensitivity loss were the average and the inferior sector measurements. The study by Ohkubo et al.[28] also found the strongest structure–function correlations to be with

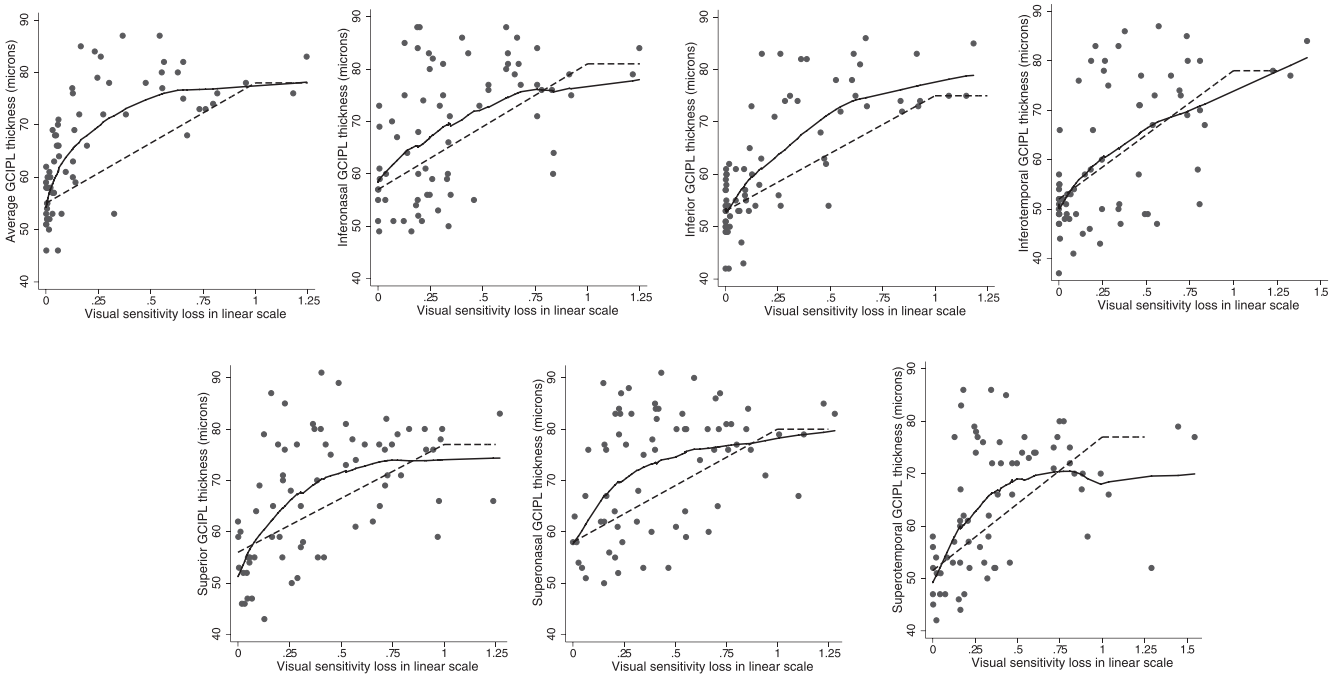

Figure 2. Linear model showing the relationship between ganglion cell–inner plexiform layer (GCIPL) thickness parameters and corresponding sector visual sensitivity loss in linear scale. *Solid black line* represents the lowess curve fitting our data. *Dashed line* represents the simple linear model fit to the data.

inferior sectors when they evaluated the GCIPL measurements against the total deviation numeric values. A similar study evaluating the relationship between GCIPL thickness and visual sensitivities on microperimetry also found stronger structure–function correlations with inferior compared to the superior sectors.[33] Inferior sectors are also the ones reported to have greater ability to diagnose perimetric glaucoma.[3–8] These are also the sectors at the macula that are more vulnerable and that manifest structural changes earlier in glaucoma as demonstrated by Hood et al.[31] These may be the reasons for a stronger structure–function relationship in the inferior GCIPL sectors. However, it is also useful to note that the differences in structure–function associations in different sectors may in part be due to the number of data points close to normal values, as opposed to local differences in the strength of an underlying relationship.

Different investigators have used different methodologies to evaluate the structure–function relationship in glaucoma. Garway-Heath et al.[10] found that the visual sensitivity expressed in linear scale defined the structure–function relationship better than visual sensitivities expressed as a dB scale. Bowd et al.[11] showed that a linear fit between structure and function with visual sensitivity expressed as a dB scale was comparable to a logarithmic fit in describing the structure–function relationship. Hood and Kardon[22] showed that a simple linear model can describe the structure–function relationship well. Previous studies have used this model to evaluate the structure–function relationship using RNFL,[18,20] inner retinal,[20] and also GCIPL thickness[19,33] measurements at the macula. This model uses visual sensitivity loss as determined on the total deviation numeric plot as the functional measure, and not the visual threshold as has been used in most of the other studies. The total deviation numeric plot adjusts the visual sensitivity loss according to the age of the subject. In this way the age-related variability in the functional measurement is minimized. For the GCIPL measurements, though there are no age-corrected values, the change with age has been reported to be small.[36] We also used lowess curves to estimate the structure–function relationship. The advantage of the lowess curve is that it does not need the specification of a function to model the relationship in a given sample. The shape of the lowess curves and the predicted curve from the Hood and Kardon[22] model shows the lag between structural and functional components in glaucoma. In early stages of glaucoma, the decline in GCIPL thickness is rapid and there is a lag in the visual sensitivity loss. But as the glaucoma damage becomes severe, GCIPL thickness reaches a base level beyond which only the visual sensitivity declines. The base level noted in our study ranged from 49 μm (63% of the thickness in control subjects) in the inferotemporal GCIPL sector to 58 μm (76% of the thickness in control subjects) in the superotemporal sector. A possible limitation in the estimation of b from our data is that the number of eyes with a mean visual sensitivity loss of >15 dB in different GCIPL sectors ranged from as low as 4 (in superotemporal sector) to as high as 24 (in inferior sector). Raza et al.[19] have also reported GCIPL base level values of 50% to 80% of the control values at different eccentricities in their small sample of glaucomatous eyes. The simple linear model fitted our data reasonably well. However, compared with the lowess curves, the predicted curves seemed to overestimate structural damage in eyes with moderate VF loss. Raza et al.[19] also noticed a systematic bias with the linear model but unlike what was seen in our study, they found that the model underestimated the structural damage in eyes with early VF sensitivity loss. Our results may be partly due to an overestimation of the visual sensitivity loss in our data. On inspection of the VFs of our study, we found that the total deviation probability plots of most of the VFs were worse than the pattern deviation plots in spite of acceptable reliability indices and media clarity. It is important to note that the simple linear model was initially developed for evaluating the structure–function relationship with the RNFL thickness. Therefore more work may be needed to refine the model for structure–function evaluation at the macula and to evaluate the reasons for discordance between the actual data and the model in certain situations.

All the glaucomatous eyes in our study had a VF defect on 10-2 VFs. We did not include any glaucomatous eyes that had normal 10-2 VF results. This may have biased the structure–function associations in our study. Therefore the results of our study must be applied to glaucomatous eyes showing defects involving the central 10° of the VF and not to glaucomatous eyes with defects sparing the central VF. Also, more than half of the glaucomatous eyes in our study had a MD worse than −12 dB. It is important to note that in eyes with such advanced glaucoma, the OCT measures are already close to the end of the dynamic range of the instrument and are less representative of axonal content, and the variability of perimetry measures is also large in and around the scotoma.

In conclusion, we found a good structure–function relationship between the GCIPL thickness at the macula measured on SDOCT and visual sensitivity loss measured on 10-2 VFs, with the average and inferior sector GCIPL thickness measurements showing the strongest relationship.

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