Comparing the Structure–Function Relationship at the Macula With Standard Automated Perimetry and Microperimetry

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With the advent of spectral-domain optical coherence tomography (SDOCT), imaging the inner retinal layers at the macula has evolved as a useful modality to assess the structural damage in glaucoma.1–9 Standard automated perimetry (SAP) has been the preferred method to evaluate the functional defects in the macular region in glaucoma.

In addition to SAP, another relatively newer method of estimating visual sensitivities at retinal points is microperimetry (MP). Microperimetry, which is also known as fundus perimetry, assesses visual sensitivity while directly examining the ocular fundus. Microperimetry results are relatively independent of eye movements and directly related to the stimulated area.10 Therefore, the visual field (VF) sensitivities measured by MP are supposed to have better spatial localization. A few earlier studies comparing SAP with MP have reported better ability of MP to detect VF defects compared with SAP. In 20 glaucomatous eyes with paracentral VF defects (defects involving the central 10° of VF on a 24° test), Lima et al.11 found that the visual sensitivities of MP in the central 10° of VF not only correlated significantly with those from SAP, but also detected abnormal areas of retinal sensitivity in quadrants with normal SAP values. They also found that in 75% of the areas showing abnormal visual sensitivity with MP and normal sensitivity with SAP there was a corresponding reduction in macular thickness on time domain OCT.11 In another previous study, Orzalesi et al.12 found reduction in visual sensitivities with MP in areas of localized retinal nerve fiber layer (RNFL) defects but the SAP results were normal. From these previous studies, it appears that the structure–function relationship between the structural and the visual sensitivity parameters of the macula may be better with MP compared with SAP. However, there are no studies, which have directly compared the structure–function relationship with SAP and MP.

The purpose of our study was to compare the structure–function relationship in glaucoma using the macular ganglion cell-inner plexiform layer (GCiPL) thickness measured with SDOCT and visual field sensitivities measured using standard automated perimetry (SAP) and microperimetry (MP) at the macula in glaucoma. The methods involved evaluating the structural changes using SDOCT and functional changes at macula in glaucoma.

METHODS

Subjects for the current analysis were recruited from a prospective, cross-sectional study performed at a tertiary eye care center between January 2015 and April 2015 to evaluate the structural and functional changes at macula in glaucoma. The methods involved evaluating the structural changes using SDOCT and functional changes using SAP and MP.
Table. Structural and Functional Characteristics of the Participants

<table>
<thead>
<tr>
<th></th>
<th>Control Group (45 Eyes of 29 Subjects)</th>
<th>Glaucoma Group (60 Eyes of 45 Subjects)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>49.2 ± 12.7</td>
<td>54.9 ± 11.6</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>GCIP parameters (μm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superotemporal thickness</td>
<td>77 (73, 81)</td>
<td>64 (52, 76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Superior thickness</td>
<td>77 (74, 83)</td>
<td>69 (56, 79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Superonasal thickness</td>
<td>80 (76, 84)</td>
<td>77 (64, 84)</td>
<td>0.02</td>
</tr>
<tr>
<td>Inferonasal thickness</td>
<td>79 (76, 83)</td>
<td>72 (57, 81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inferior thickness</td>
<td>76 (73, 83)</td>
<td>65 (53, 76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inferotemporal thickness</td>
<td>79 (73, 83)</td>
<td>59 (50, 73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Average thickness</td>
<td>77 (75, 83)</td>
<td>68 (55, 78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Standard automated perimetry parameters (dB)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD</td>
<td>−3.4 (−5.2, −1.4)</td>
<td>−7.6 (−16.2, −3.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pattern standard deviation</td>
<td>1.4 (1.2, 2.9)</td>
<td>4.0 (1.5, 10.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Superotemporal sensitivity loss</td>
<td>0.4 (−2.1, 2.1)</td>
<td>−1.9 (−4.6, 0.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Superior sensitivity loss</td>
<td>0.0 (−2.7, 1.7)</td>
<td>−1.5 (−4.1, 0.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Superonasal sensitivity loss</td>
<td>−0.0 (−3.4, 1.7)</td>
<td>−1.2 (−3.4, 1.0)</td>
<td>0.15</td>
</tr>
<tr>
<td>Inferonasal sensitivity loss</td>
<td>0.0 (−2.0, 2.0)</td>
<td>−1.5 (−4.8, 0.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Inferior sensitivity loss</td>
<td>0.0 (−1.0, 1.9)</td>
<td>−2.4 (−17.2, 0.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inferotemporal sensitivity loss</td>
<td>0.2 (−2.2, 1.7)</td>
<td>−3.0 (−12.4, −0.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Average sensitivity loss</td>
<td>0.7 (−2.3, 2.0)</td>
<td>−1.7 (−6.7, −0.1)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Microperimetry parameters (dB)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superotemporal sensitivity loss</td>
<td>0.1 (−3.2, 1.8)</td>
<td>−3.4 (−6.9, −0.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Superior sensitivity loss</td>
<td>−0.0 (−2.1, 2.2)</td>
<td>−1.8 (−5.7, 0.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Superonasal sensitivity loss</td>
<td>0.0 (−2.8, 2.8)</td>
<td>−1.8 (−4.2, 1.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>Inferonasal sensitivity loss</td>
<td>0.0 (−3.9, 2.2)</td>
<td>−2.9 (−8.5, −0.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inferior sensitivity loss</td>
<td>−0.0 (−1.9, 2.3)</td>
<td>−4.7 (−24.6, −1.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inferotemporal sensitivity loss</td>
<td>−0.0 (−3.6, 1.8)</td>
<td>−5.6 (−20.5, −1.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Average sensitivity loss</td>
<td>0.0 (−3.2, 1.7)</td>
<td>−3.4 (−6.0, −0.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

All values are represented as median and interquartile range unless otherwise specified.

* Mean ± SD.

Informed consent was obtained from all participants and the Ethics Committee of L V Prasad Eye Institute (Banjara Hills, Hyderabad, India) approved the study methodology. All methods adhered to the tenets of the Declaration of Helsinki for research involving human subjects.

Inclusion criteria were age 18 years or older, best corrected visual acuity (BCVA) of 20/40 or better and refractive error within ±5 diopters (D) sphere and ±3 D cylinder. Exclusion criteria were presence of any media opacities that affected SDOCT scans and SAP and MP 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, (BCVA) measurement, slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, dilated fundus examination, central 10° VF examination with SAP and MP and SDOCT imaging with Cirrus high definition OCT (HD-OCT; Carl Zeiss Meditec, Inc., Dublin, CA, USA).

Spectral-domain OCT examination was performed with Cirrus HD-OCT (software version 6.0). The macular Cube 200 × 200 protocol was used to image the macula. This protocol has been explained in detail previously. Ganglion cell analysis (GCA) is a procedure that measures the GCIP thickness within a 14.13 mm² 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 GCIP thickness across the entire elliptical annulus and the thickness at six 60° sectors of the elliptical annulus. Scans with a signal strength less than 6 and segmentation errors were labelled as “poor quality” images and excluded from the analysis.

Standard automated perimetry examination of the macula 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 or equal to 20% and false positive and negative response rates were less than or equal to 15%.

Microperimetry examination of the macula was performed using the Macular Integrity Assessment (MAIA; CenterVue, Padova, Italy) instrument. The protocol used was a 10-2 grid, which tests the visual sensitivity in the central 10° of the retina using 68 points, similar to the 10-2 program of SAP. The stimulus size was equal to the Goldmann size III stimulus of SAP. Background luminance was set at 4 apostilb (1.27 cd/m²), with a maximum luminance of 1000 apostilb (318 cd/m²) and a stimulus dynamic range of 36 dB. Visual sensitivities were estimated using a 4-2 staircase threshold strategy. Microperimetry results were considered reliable if the reliability index was greater than 70% (percentage of control points projected on the optic nerve, which were not seen by the subject) and the fixation was stable (more than 75% of the subject) and the fixation was stable (more than 75% of the fixation points were located within a 2° diameter circle centered in the gravitational center of all fixation points).

To evaluate the GCIP thickness and retinal sensitivity at similar locations across the macula, we used the structure–function correlation map described previously using the GCIP sectors of Cirrus HD-OCT and the 10-2 program of SAP and MP. This map also considered the displacement of the RGCs at the macula by using equations derived from the...
histologic analysis to approximate the location of the RGCs with each SAP/MP test point. Visual sensitivities at all 68 points of SAP and MP were first converted from the decibel scale to a linear scale (reciprocal of Lambert scale) using the following formula.

\[ \frac{1}{\text{Lambert}} = (10)^{0.1 \times \text{dB}} \]  

The values from all test points within the VF sectors corresponding to the anatomic sectors described above were then averaged. The average visual sensitivity per sector was converted back to the decibel scale for the analysis. This procedure has been explained in detail previously. The sectors of SAP were flipped horizontally and vertically to correlate with the sectors of HD-OCT and MP.

Glaucoma patient group consisted of a consecutive series of eligible glaucoma patients attending the hospital during the study period. Glaucoma was diagnosed in all these eyes by the treating glaucoma specialist based on the characteristic optic disc findings of neuroretinal rim thinning, notching, or localized or diffuse RNFL defects. The control subject group consisted of subjects attending the hospital for a routine eye examination, for refractive error assessment or were spouses and friends of the recruited patients. The control subjects had no family history of glaucoma, no history of raised IOP in the past, normal anterior, and posterior segments as assessed by experts on clinical examination and IOP of less than or equal to 21 mm Hg. Both the VF examinations (SAP and MP) and the SD-OCT examination were done on the same day in all the subjects.

**STATISTICAL ANALYSIS**

Descriptive statistics included the mean and standard deviation for normally distributed variables and median and interquartile range (IQR) for nonnormally distributed variables.

Structure–function relationship between the GCIPL parameters of HD-OCT and visual sensitivities of SAP and MP were evaluated using the model proposed by Hood and Kardon. Details of the model proposed by Hood and Kardon are explained elsewhere. This model makes some basic assumptions to evaluate the structure–function relationship. It proposes that the structural thickness, \( R \), measured with OCT (GCIPL thickness here) is made up of two components, thickness due to retinal ganglion cells, 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,

\[ R = s_o + b \]  

It also proposes that visual sensitivity decreases, as the signal \( s_o \) decreases, but the residual \( b \) does not change. So Equation 2 is written as

\[ R = s_o \times 10^{-0.1D} + b, \]  

where \( D \) is the loss of visual sensitivity on dB scale. Visual sensitivity loss in each sector was calculated by subtracting the average visual sensitivity at each sector in the control group from the observed visual sensitivity in each sector. Base level or

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**FIGURE 1.** Hood and Kardon models showing the relationship between GCIPL thickness parameters in different sectors (a-g) and corresponding sector visual sensitivity loss in decibel scale on SAP and MP.
b was taken as 60% of the GCIPL thickness of the median value in the control subjects for a particular sector. The 5th and 95th percentile values of the model were plotted as proposed by Hood and Kardon. To compare structure-function relationship with SAP and MP, we calculated the number of data points falling outside the 5th and the 95th percentile values of the Hood and Kardon model with each of the perimeters.

Statistical analyses were performed using commercial software (Stata ver. 12.1; StataCorp, College Station, TX, USA). A P value of less than 0.05 was considered statistically significant.

RESULTS

One hundred twenty-seven eyes of 80 participants (53 eyes of 31 control subjects and 74 eyes of 49 glaucoma patients) underwent GCIPL imaging with HD-OCT and macular visual sensitivity assessment with SAP and MP. After excluding six eyes with poor quality HD-OCT, six eyes with unreliable SAP, eight eyes with unreliable MP, one eye with poor quality HD-OCT and unreliable MP, and one eye with unreliable MP and SAP results, the final analysis consisted of 105 eyes of 70 participants. The Table shows the age, GCIPL thickness, visual sensitivity loss on SAP and MP of the glaucoma and the control groups. Control subjects were significantly younger than the glaucoma patients. The mean deviation (MD) of the 24-2 SAP of the glaucoma patients ranged from 1.04 to 32.84 dB (median: 7.61 dB, IQR: 4.29 to 18.73 dB). Based on the MD of the 24-2 SAP, 9 eyes had preperimetric, 15 early (MD of better than 6 dB), 15 moderate (MD between -6 and -12 dB), and 21 severe (MD of worse than -12 dB) VF loss.

Figures 1a–g show the structure–function model proposed by Hood and Kardon fit to the macular sectors with SAP and MP separately. The base level b was calculated as 60% of the median GCIPL thickness of the control group in each sector. The three curves in the figures, representing the median (solid line) and the 5th and 95th percentile values were plotted according to the method proposed by Hood and Kardon.1 The central solid line in the figures was derived by joining the median GCIPL thickness of healthy subjects in each sector with 60% of this value, respectively. The dashed lines above and below the solid line were derived by connecting the 5th and 95th percentile values of GCIPL thickness of normal subjects in each sector with 60% of these values respectively.

Figures 2a–g are Venn diagrams showing the number of points falling outside the 5th and 95th percentile values of the Hood and Kardon model in different sectors (a–g) with SAP and MP.

DISCUSSION

Determining the strength of structure–function relationships in glaucoma with different methods of structural and functional assessments has significant clinical implications. This not only helps in better understanding of structural and functional

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**Figure 2.** Venn diagrams showing the number of points falling outside the 5th and 95th percentile values of the Hood and Kardon model in different sectors (a–g) with SAP and MP.
progression in glaucoma but also in deciding appropriate diagnostic tests during the follow-up in glaucoma patients. Though imaging the inner retinal layers at macula has evolved as a useful modality in diagnosing glaucoma, studies evaluating the structure-function relationship at macula are limited. The GCIPL studies with SDOCT used the RNFL thickness at the papillomacular bundle to correlate with macular function. However, the RNFL of the temporal region has been shown to demonstrate a high degree of variability, even in healthy individuals. Multiple studies subsequently evaluated the structure-function relationship at the macula using the inner retinal layer thickness at macula obtained with SDOCT. Inner retinal layer thickness at macula generally included the RNFL, ganglion cell layer and the inner plexiform layer thickness (together called ganglion cell complex [GCC]). Measuring specifically the ganglion cell and inner plexiform layer thickness at macula is expected to improve the structure-function relationship in glaucoma and a few recent studies evaluated the same. The other issue to note is that most of the previous studies used 24-2 program of SAP, unlike the 10-2 program used in our study, to evaluate the functional changes at macula. However, 24-2 program estimates retinal sensitivity in the central 10° of visual field using only 16 points, which are 6° apart while the 10-2 program evaluates the central 10° of VF using 68 test points that are 2° apart. The sampling density of 24-2 program to evaluate VF scotoma at macula is therefore inadequate. A study by Schiefer et al. showed better detection of VF defects in eyes with suspected glaucoma when closely spaced test points were used. Another study by Traynis et al. reported field defects on 10° program in eyes with no defects on 24° VF program. Also, the locations of the ganglion cells stimulated by the central 24-2 VF test points are farther from the fovea because the ganglion cells in the fovea are displaced. We therefore evaluated the structure of macula using the GCIPL thickness measurements and the function using the visual sensitivities measured at the macula across 68 points which were 2° apart.

Though different investigators have used different methodologies to evaluate the structure-function relationship in glaucoma, Hood and Kardon showed that a simple linear model can describe the structure-function relationship well. We used this model to study the structure-function relationship. Multiple previous studies have also used this model to evaluate the structure-function relationships with RNFL, inner retinal, and also GCIPL thickness measurements. This model uses visual sensitivity loss as determined on the total deviation numeric plot of SAP as the functional measure. However, as the MP does not provide the age adjusted loss of visual sensitivity at different points (like the total deviation map of SAP), we derived the visual sensitivity loss in each sector of SAP and MP by subtracting the average visual sensitivity in each sector in healthy subjects from the actual visual sensitivity. The predicted curve from the Hood and Kardon 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 increases in severity, GCIPL thickness reaches a base level beyond which only the visual sensitivity declines.

Though SAP is the standard procedure for assessing the visual sensitivities at macula, MP, a relatively newer perimeter, has been reported to demonstrate better ability to detect VF defects compared with the SAP. However, in our present study to compare the structure-function relationships with SAP and MP in glaucoma, we found that both methods of visual sensitivity measurement demonstrated a similar relationship with the GCIPL measurement at the macula. Though there are studies evaluating the structure-function relationship of GCIPL with SAP and MP separately using the Hood and Kardon model, there are no studies comparing the two. Raza et al. evaluated the structure-function relationship using GCIPL thickness and 10-2 SAP 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. In a previous study, we also had evaluated the structure-function relationship using GCIPL thickness and 10-2 SAP. All the glaucoma patients included in our previous study had VF defects on 24-2 and 10-2 SAP. Both the study by Raza et al. and our previous study had found that the fit of the Hood and Kardon to the data was reasonable. Similar to the previous studies with SAP, Sato et al. evaluated the structure-function relationship using GCIPL thickness and the visual sensitivities in the central 10° field measured using MP and found that the Hood and Kardon model fitted the data reasonably well.

Though Hood and Kardon model has been shown to fit the structure-function data of the GCIPL thickness and VF loss over the central 10° field reasonably well, it is important to note a few possible limitations of the model when used in our study. In our previous study, we had reported that the model overestimated the structural damage in eyes with moderate VF loss. Raza et al. also had noticed a systematic bias, with the model underestimating the structural damage in eyes with early visual sensitivity loss. It is important to note that the model was initially developed for evaluating the structure-function relationship with the RNFL thickness and the visual sensitivity loss on 24-2 SAP program. Therefore, more work may be needed to refine the model for structure-function evaluation at the macula. As the model was developed for SAP, there may also be an inherent bias against MP when the model was used to compare the structure-function relationship with SAP and MP.

In conclusion, we found that the visual sensitivity measurements of both SAP and MP demonstrated a similar relationship with the GCIPL measurements of SDOCT at the macula in glaucoma.

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References


