Association of Glaucoma-Related, Optical Coherence Tomography–Measured Macular Damage With Vision-Related Quality of Life

Alisa J. Prager, MD, MPH; Donald C. Hood, PhD; Jeffrey M. Liebmann, MD; C. Gustavo De Moraes, MD, MPH; Lama A. Al-Aswad, MD, MPH; Qi Yu, MD; George A. Cioffi, MD; Dana M. Blumberg, MD, MPH

IMPORTANCE Little is known about the association between structural macular damage and self-reported visual function of people with glaucoma.

OBJECTIVE To determine the association between vision-related quality of life among patients with primary open-angle glaucoma with structural macular retinal ganglion cell plus inner plexiform layer (RGC+IPL) loss identified by spectral-domain optical coherence tomography (SD-OCT) machine-generated deviation maps and thickness measurements.

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional prospective study was conducted from March 1, 2014, to March 30, 2015, at the Department of Ophthalmology at Columbia University Medical Center. The participants were 107 patients who were enrolled in the study and represented the entire range of glaucomatous damage. All 214 eyes of the 107 participants underwent 10-2 visual field tests and SD-OCT scans, and all participants completed the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25). They also received ophthalmologic examination, including medical history review, best-corrected visual acuity, slitlamp biomicroscopy, intraocular pressure measurement, gonioscopy, dilated ophthalmoscopy, and standard automated perimetry. Macular RGC+IPL loss was determined by diffuse or focal patterns on SD-OCT-generated deviation maps (probability map that compared patients with aged-matched normative database) and thickness measurements.

MAIN OUTCOMES AND MEASURES Regression analyses to assess the association of NEI VFQ-25 scores (score range: 41.9-99.5; higher scores indicate better functioning) with patterns of RGC+IPL loss and with RGC+IPL thickness measurements.

RESULTS Of the 107 patients, 48 (45%) were men and the mean (SD) age was 65 (11) years. The self-reported race/ethnicity of participants consisted of 45 (46%) black, 47 (48%) white, and 6 (6%) “other” individuals. In the univariable analyses, patients with diffuse macular RGC+IPL loss had mean composite Rasch-calibrated NEI VFQ-25 scores that were 6.15 points lower than the scores of patients with focal damage ($\beta = -6.15$; 95% CI, $-11.7$ to $-0.59$; $P = .03$). The effect remained significant even after controlling for mean RGC+IPL thickness ($\beta = -7.64$; 95% CI, $-14.2$ to $-1.03$; $P = .02$).

CONCLUSIONS AND RELEVANCE Characteristic patterns of glaucoma-related macular RGC+IPL loss appeared to be more important predictors of vision-related quality of life than thickness measures, with diffuse RGC+IPL loss as an indicator for diminished vision-related quality of life.
Glaucoma was traditionally thought to affect the peripheral visual field (VF). However, a growing body of evidence has shown that early glaucoma is associated with structural macular (central ±8°) damage to retinal ganglion cells and that a strong structure-function correlation can be demonstrated during testing of the central VF. Macular functional damage is best detected using the 10-2 VF strategy because small paracentral defects may fall in between the 6° grid of the 24-2 VF.

A recent report found a stronger association between vision-related quality of life (VRQoL) and binocular central 10-2 VFs compared with 24-2 VFs. Despite early evidence that the 10-2 VF is better correlated with VRQoL than the 24-2 VF, little is known about the direct association between QoL and macular structural damage, as measured by spectral-domain optical coherence tomography (SD-OCT) macular retinal ganglion cell plus inner plexiform layer (RGC+IPL) thickness. This study investigated the association between glaucomatous macular RGC+IPL loss and self-reported visual function as measured by the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25), to determine if SD-OCT macular structural change can be used as a surrogate measure for subjectively assessing VRQoL.

Methods

Study Design

Patients with glaucoma were enrolled in a prospective study conducted at the Department of Ophthalmology at Columbia University Medical Center, New York, New York, from March 1, 2014, to March 30, 2015. Cross-sectional data analysis was performed from May 1, 2016, to October 31, 2016.

The institutional review board of Columbia University Medical Center approved the study and its methods, and the study adhered to the regulations of the Health Insurance Portability and Accountability Act. Written informed consent was obtained from all participants, and all study methods adhered to the tenets of the Declaration of Helsinki.

All eligible consecutive patients underwent a comprehensive ophthalmologic examination, including medical history review, best-corrected visual acuity, slitlamp biomicroscopy, intraocular pressure measurement, gonioscopy, dilated ophthalmoscopy, and standard automated perimetry (SAP) (standard 24-2 and 10-2 Swedish Interactive Threshold Algorithm; Carl Zeiss Meditec, Inc). Individuals were included if they had bilateral primary open-angle glaucoma with perimetric damage in at least 1 eye as determined by a glaucoma specialist, the cognitive ability to complete a reliable questionnaire, and visual acuity of 20/30 or better. Individuals were excluded if they had any ocular or systemic disease that could affect the optic nerve or VF or if they could not perform a reliable VF, defined as less than 33% fixation losses or false-negative errors and less than 15% false-positive errors.

Participants were classified as having glaucoma on the basis of characteristic optic nerve damage on stereoscopic photographs and a repeatable abnormal VF in at least 1 eye on 2 consecutive 24-2 fields. Abnormal SAP was defined as a pattern SD with P < .05 and/or glaucoma hemifield test results outside normal limits.

VRQoL Questionnaires

Interviewers administered the NEI VFQ-25, which evaluates dimensions of self-reported health relevant to patients with chronic eye diseases. The NEI VFQ-25 consists of 25 questions representing 11 subscales plus a single-item, general health-rating question. The subscales are General Vision, Near and Distance Vision Activities, Ocular Pain, Vision-Related Social Function, Vision-Related Role Function, Vision-Related Mental Health, Vision-Related Dependency, Driving Difficulties, Color Vision, and Peripheral Vision. Each subscale consists of 1 to 4 items. Furthermore, participants answered a survey with information regarding their age, sex, and self-reported race/ethnicity.

Monocular and Binocular VFs

Estimates of binocular mean deviation for the 10-2 VF were calculated from the total deviation plots of both eyes according to the best-location algorithm described by Nelson-Quigg and colleagues. With this approach, the binocular VF was a composite of the more sensitive of the 2 VF locations for each eye.

SD-OCT Scan

The SD-OCT scan (Cirrus SD-OCT Macular Cube 512 × 128 scan; Carl Zeiss Meditec, Inc) was used to measure the RGC+IPL thickness. Because the boundary between the RGC and IPL was anatomically indistinct on some scans, the combined thickness was used to measure the health of RGCs. Images were acquired by a trained ophthalmic photographer. All scans were reviewed and images were excluded if there was motion or blinking artifacts, incorrect placement of the measurement circle, segmentation error, or poor image quality (signal strength <6). RGC+IPL thickness was analyzed using 8 measures provided by the instrument software (Cirrus SD-OCT Macular Cube 512 × 128 scan; Carl Zeiss Meditec, Inc).

Thickness Measurement

The 8 instrument-generated thickness measures included the 6 sectors (superior, superior nasal, superior temporal, inferior, inferior nasal, and inferior temporal).
rior, inferior nasal, and inferior temporal) as well as the mean and minimal thicknesses. In addition, the corresponding sectors were averaged to calculate the superior hemifield sectors (superior, superior nasal, and superior temporal) and inferior hemifield sectors (inferior, inferior nasal, and inferior temporal).

For each patient, the “better” and “worse” eyes were defined by the higher mean and lower mean RGC+IPL thickness measures, respectively. As an extension of the binocular VF, the integrated maximum RGC+IPL thickness was calculated by averaging the highest RGC+IPL thickness measures from each of the 6 sectors of each eye (Figure 1). A similar method was used to calculate the integrated superior hemifield RGC+IPL and the integrated inferior hemifield RGC+IPL (Figure 1). Furthermore, the integrated minimum RGC+IPL thickness was calculated by averaging the lowest RGC+IPL thickness measures from each of the 6 sectors of each eye.

Patterns of RGC+IPL Loss
Recent data from Hood and colleagues\textsuperscript{11,12} have demonstrated that glaucoma is associated with both diffuse and localized patterns of macular RGC+IPL loss. As exemplified in Figure 2, similar overall mean RGC+IPL thickness measurements may occur in eyes with different patterns of RGC+IPL loss. The eye with the focal defect (Figure 2A) and the eye with the diffuse loss (Figure 2B) had the same mean RGC+IPL thickness of 67 μm. Thus, RGC+IPL thickness measures generated by the software algorithm will not adequately capture topographic information.

According to the Hood model,\textsuperscript{2,12} focal macular damage has characteristic patterns. Using this model, we categorized patients with macular damage of the better eye on the basis of the shape and location of RGC+IPL loss that are referred herein as the “pattern” of RGC+IPL loss. Macular RGC+IPL loss was first identified in a previous work by Kim and colleagues,\textsuperscript{13} who defined RGC+IPL loss as an area of contiguous color-coded pixels at least 10 superpixels in area and more than a boundary of 1 superpixel away from the inner annulus. Focal loss was defined as damage to the superotemporal or inferotemporal RGC+IPL sectors of the macula adjacent to the horizontal raphe\textsuperscript{2,12} (arrowhead in Figure 2A), with damage at the 1% or 5% level of the Cirrus SD-OCT (Carl Zeiss Meditec, Inc) reference database of healthy eyes and with a corresponding fusi-form or islandlike 1% defect seen on the deviation map (Figure 2A). In contrast, diffuse loss was defined as diffuse and circular in either or both hemifields, with RGC+IPL loss at the 1% or 5% level on the deviation map (Figure 2B).

Statistical Analyses
Rasch analysis was performed to obtain final estimates of person-measures, which express patients’ perception of their own degree of impairment as measured by the NEI VFQ-25. These linear Rasch-calibrated scores were computed and used for subsequent parametric statistical analyses. Rasch analysis was performed using Andrich rating-scale models to obtain the estimates of the required ability of each item, perceived ability of each patient, and thresholds for each response category. Rasch analysis locates item difficulty and person ability on a logit (log odds) scale, which was linearly rescaled to range from 0 to 100, with higher scores indicating functioning.

A scatterplot was created to show the association between the RGC+IPL thickness (x-axis) and the NEI VFQ-25 score (y-axis) (Figure 3). Univariable and multivariable linear regression analyses using ordinary least squares were conducted to determine the association among quantitative RGC+IPL thickness measures, patterns of RGC+IPL loss, composite Rasch-calibrated NEI VFQ-25 scores of patients with glaucoma, and binocular 10-2 VFs. Linear regression was used to calculate P values, and P = .05 was used to indicate statistical significance.

Statistical analyses were performed using Winsteps, version 3.81.0 (Winsteps) and Stata, version 14 (StataCorp).

Results
This study included 214 eyes of 107 patients with glaucomatous optic discs and VF loss on 24-2 Swedish Interactive Threshold Algorithm SAP. Of the 107 patients, 48 (45%) were men, and the mean (SD) age was 65 (11) years. The self-reported race/ethnicity of participants included 45 (46%) black, 47 (48%) white, and 6 (6%) “other” individuals. Participant demographics as well as VF and OCT measurements are listed in the Table.

Pattern of RGC+IPL Loss
In the univariable analyses, patients with diffuse macular RGC+IPL loss had mean composite Rasch-calibrated NEI VFQ-25 scores that were 6.15 points lower than the scores of patients with focal macular RGC+IPL loss (β = −6.15; 95% CI, −11.7 to −0.59; P = .031). The association remained even after controlling for mean RGC+IPL thickness (β = −7.64; 95% CI, −14.2 to −1.03; P = .024).
There was no detectable association between NEI VFQ-25 scores and any of the RGC+IPL thickness measures despite the potential mediating effect of binocular 10-2 VF (eTable 1 in the Supplement). Binocular 10-2 VF mean sensitivity was associated with all RGC+IPL thickness measures, except for the minimum RGC+IPL thickness of the worse eye (eTable 2 in the Supplement). (Mean RGC+IPL was correlated with binocular 10-2 VF: better eye $\beta = 0.12$ dB; 95% CI, 0.056-0.18; $P < .001$; $R^2 = 16$%; integrated eye $\beta = 0.12$ dB; 95% CI, 0.059-0.18; $P < .001$; $R^2 = 16$%; worse eye $\beta = 0.07$ dB; 95% CI, 0.016-0.12; $P < .012$; $R^2 = 8$%). Binocular 10-2 VF mean sensitivity was correlated with NEI VFQ-25 composite scores: $\beta = 1.14$; 95% CI, 0.47-1.82; $P = .001$; $R^2 = 13$%). We were unable to identify any associations between NEI VFQ-25 scores and RGC+IPL thickness measures, whether tested among the entire cohort or a subset of patients with focal or diffuse patterns of macular RGC+IPL loss.

### Discussion

The present study suggests that, among those with glaucomatous macular damage, the regional distribution of RGC+IPL loss was associated with VRQoL. Specifically, participants with widespread, diffuse macular damage had lower NEI VFQ-25 scores than those with focal damage. In contrast, participant-reported VRQoL measures were not directly associated with the instrument-generated thickness measures. This was a surprising finding because previous work suggested that macular damage as measured by binocular 10-2 VF and NEI VFQ-25...
was associated with continued decline in Rasch-calibrated NEI VFQ-25 scores as 10-2 mean deviation declined.6 By extension, our study found an association between RGC+IPL thickness measures and binocular 10-2 VFs. This finding agrees with that of Raza and colleagues,1 who observed an association between a decrease in RGC+IPL thickness and SAP losses within the central 7.2° VF. Despite this, a direct association between the machine-generated RGC+IPL thickness measures and NEI VFQ-25 scores was not observed.

There are several possible explanations for why the thickness measures did not predict VRQoL. The first and most likely explanation is that the diagnostic thickness measures may not be sensitive enough to detect subtle macular damage on the RGC+IPL deviation map. As illustrated in Figure 2, participants with similar mean RGC+IPL measures may have different patterns of macular RGC+IPL loss that affect QoL differently. Second, healthy individuals and those with glaucoma may vary in baseline retinal anatomy and RGC+IPL thickness.14-16 Participants with relatively thick retinal nerve fiber layer (RNFL) at baseline may be more likely to show significant SAP sensitivity loss before statistically significant OCT RNFL loss, while the reverse may be true for those with thin or typical RNFL at baseline but relatively good SAP sensitivity.15 By extension, differences in the baseline RGC+IPL thickness may affect the association between these measurements and participant-reported outcomes. This effect is further complicated by the hypothesized association between structural and functional declines in glaucoma, which is thought to be characterized by early decline in RGC+IPL thickness that is relatively greater than visual sensitivity loss and by loss of visual sensitivity (but not of RGC+IPL) in the later stage of the disease.1,15

To date, there is limited published research on structural measures and patient-reported QoL outcomes. In a cross-sectional study, Hines and colleagues17 found that mean peripapillary RNFL thickness was not predictive of QoL scores. On the other hand, Gracitelli and colleagues18 conducted a longitudinal study and found an association between change in NEI VFQ-25 scores and change in mean binocular RNFL thickness after adjusting for baseline 24-2 VF damage. The discrepancies in these study findings may be attributable to differences in study design (cross-sectional vs longitudinal), or patient compensatory mechanisms that occur over time may play a role in patient-reported QoL. Furthermore, intra-individual comparisons (in which each person serves as his or her own control) may be better than comparisons against a standardized set of values. Longitudinal progression modeling, by comparing progression of RGC+IPL loss within individuals over time, may better account for these factors.14,18 Future studies comparing the progression of RGC+IPL loss with change in VRQoL are warranted.

Limitations

Four potential limitations to this study were identified. First, we conducted a cross-sectional study to get a fundamental understanding of the association between structural macular damage and VRQoL. Subsequent research is necessary to assess whether progression of macular damage is associated with change in QoL measures. Second, self-reported VRQoL is a multidimensional construct, and we could have strengthened the multivariable model by adding determinants of reported visual function, including age, socioeconomic status, number of glucoma medications, and comorbidities such as depression. However, we did not include these variables to compare the relative associations of structural measures with reported visual function. Although the $R^2$ values would likely increase by adding these covariates, their inclusion serves no purpose when the goal is to compare the association between OCT and VF metrics using QoL instruments in patients who underwent both tests. Third, other patient-reported surveys may have been better able to capture the effect of glaucoma on QoL.19,20 We chose the NEI VFQ-25 because it is a validated and widely used tool to assess an individual’s performance of vision-dependent tasks.20 Future investigations could look into other patient-reported QoL measures. Last, we defined diffuse vs focal macular damage in broad terms using the RGC+IPL deviation map. Future studies should consider quantifying the area and volume of RGC+IPL loss relative to NEI VFQ-25.

A better understanding of how structural and functional measures affect QoL can help clinicians assess disease severity and plan treatment.

Table. Participant and Eye Characteristics of 107 Individuals in Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Finding</th>
</tr>
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<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>65 (11)</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>48 (45)</td>
</tr>
<tr>
<td>Race/ethnicity, No. (%) (n = 98)*</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>45 (46)</td>
</tr>
<tr>
<td>White</td>
<td>47 (48)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (6)</td>
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<tr>
<td>Worse eye RGC+IPL thickness, mean (SD), μm</td>
<td></td>
</tr>
<tr>
<td>— Mean</td>
<td>62 (9)</td>
</tr>
<tr>
<td>— Range</td>
<td>6 to 7</td>
</tr>
<tr>
<td>Better eye RGC+IPL thickness, mean (SD), μm</td>
<td></td>
</tr>
<tr>
<td>— Mean</td>
<td>71 (14)</td>
</tr>
<tr>
<td>— Range</td>
<td>7 to 10</td>
</tr>
<tr>
<td>Composite Rasch-calibrated NEI VFQ-25 score, mean (SD)</td>
<td></td>
</tr>
<tr>
<td>— Range</td>
<td>89 (9)</td>
</tr>
<tr>
<td>Patterns of RGC+IPL loss (n = 93)</td>
<td></td>
</tr>
<tr>
<td>— Focal, No. (%), eyes</td>
<td>21 (19.6)</td>
</tr>
<tr>
<td>— Diffuse, No. (%), eyes</td>
<td>41 (38.3)</td>
</tr>
</tbody>
</table>

Abbreviations: MD, mean deviation; NEI VFQ-25, 25-item National Eye Institute Visual Function Questionnaire; RGC+IPL, retinal ganglion cell plus inner plexiform layer; VF, visual field.

* Nine patients did not self-identify race/ethnicity.

Conclusions

We found that patterns of macular RGC+IPL loss, rather than quantitative RGC+IPL measurements, play a role in VRQoL. The presence of diffuse macular damage on SD-OCT appears to be correlated with VRQoL, and clinicians should focus their attention on individuals with this type of damage, some of whom may benefit from low-vision assessment and aggressive glaucoma treatment.
Study concept and design: Prager, Hood, Liebmann, De Moraes, Al-Aswad, Yu, Cioffi, Blumberg. Acquisition, analysis, or interpretation of data: Prager, Liebmann, De Moraes, Al-Aswad, Yu, Cioffi, Blumberg. Drafting of the manuscript: Prager, Hood, De Moraes, Blumberg. Critical revision of the manuscript for important intellectual content: Prager, Liebmann, De Moraes, Al-Aswad, Yu, Cioffi, Blumberg. Statistical analysis: Prager, De Moraes, Blumberg. Obtained funding: Hood, Cioffi. Administrative, technical, or material support: Hood, Liebmann, Al-Aswad, Yu, Cioffi. Study supervision: Liebmann, Al-Aswad, Cioffi, Blumberg.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Hood reported receiving equipment and financial support from Topcon as well as equipment from Heidelberg. Dr Liebmann reported being a consultant to Carl Zeiss Meditec, Inc on matters unrelated to this study. No other disclosures were reported.

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