Association Between Progressive Retinal Nerve Fiber Layer Loss and Longitudinal Change in Quality of Life in Glaucoma

Carolina P. B. Gracitelli, MD; Ricardo Y. Abe, MD; Andrew J. Tatham, FRCoPhth; Peter N. Rosen, MD; Linda M. Zangwill, PhD; Erwin R. Boer, PhD; Robert N. Weinreb, MD; Felipe A. Medeiros, MD, PhD

**IMPORTANCE** Evaluation of structural optic nerve damage is a fundamental part of diagnosis and management of glaucoma. However, the relationship between structural measurements and disability associated with the disease is not well characterized. Quantification of this relationship may help validate structural measurements as markers directly relevant to quality of life.

**OBJECTIVE** To evaluate the relationship between rates of retinal nerve fiber layer (RNFL) loss and longitudinal changes in quality of life in glaucoma.

**DESIGN, SETTING, AND PARTICIPANTS** Observational cohort study including 260 eyes of 130 patients with glaucoma followed up for a mean (SD) of 3.5 (0.7) years. All patients had repeatable visual field defects on standard automated perimetry (SAP) at baseline. The 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) was performed annually, and spectral-domain optical coherence tomography and SAP were performed at 6-month intervals. A joint model was used to investigate the association between change in NEI VFQ-25 Rasch-calibrated scores and change in RNFL thickness, adjusting for confounding socioeconomic and clinical variables.

**MAIN OUTCOMES AND MEASURES** Association between change in binocular RNFL thickness (RNFL thickness in the better eye at each point) and change in NEI VFQ-25 scores.

**RESULTS** Progressive binocular RNFL thickness loss was associated with worsening of NEI VFQ-25 scores over time. In a multivariable model adjusting for baseline disease severity and the rate of change in binocular SAP sensitivity, each 1-μm-per-year loss of RNFL thickness was associated with a decrease of 1.3 units (95% CI, 1.02-1.56) per year in NEI VFQ-25 scores (P < .001). After adjusting for the contribution from SAP, 26% (95% CI, 12%-39%) of the variability of change in NEI VFQ-25 scores was associated uniquely with change in binocular RNFL thickness. The P value remained less than .001 after adjusting for potential confounding factors.

**CONCLUSIONS AND RELEVANCE** Progressive binocular RNFL thickness loss was associated with longitudinal loss in quality of life, even after adjustment for progressive visual field loss. These findings suggest that rates of binocular RNFL change are valid markers for the degree of neural loss in glaucoma with significant relationship to glaucoma-associated disability.
Glaucma is a leading cause of irreversible loss of vision.\(^1\) Although blindness is the most feared consequence of glaucoma, there is growing evidence that even relatively mild disease may have a significant impact on quality of life (QoL). The impact of glaucoma on vision-related QoL has previously been investigated using questionnaire-based self-reported assessments such as the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25).\(^2\)\(^-\)\(^4\) Cross-sectional studies using the NEI VFQ-25 have demonstrated an association between glaucomatous visual field loss and QoL, but the reported relationships have been generally weak.\(^5\)\(^-\)\(^7\) A possible reason for this is that patients with slowly progressive glaucomatous damage may adapt to reduce the impact of visual loss on activities of daily living. In fact, a study by Medeiros et al\(^8\) demonstrated that patients with faster decline in binocular visual field (BVF) sensitivity had worse deterioration in NEI VFQ-25 scores during follow-up.

Despite visual field testing being the most common method to monitor glaucomatous progression, some patients with glaucoma may develop evidence of structural damage to the optic nerve and retinal nerve fiber layer (RNFL) in the absence of detectable changes on standard perimetry.\(^9\)\(^-\)\(^14\) Although evaluation of structural changes is a fundamental part of the diagnosis and management of glaucoma, the relationship between clinically detectable optic nerve and RNFL changes and visual impairment, however, is not well understood.\(^15\) To our knowledge, only a few cross-sectional studies have addressed this subject.\(^16\)\(^,\)\(^17\) However, investigations of this relationship using cross-sectional data are limited by the wide interindividual variability in subjective perceptions about QoL and by possible effects of compensatory mechanisms, as previously described.\(^18\) To our knowledge, there have not been any reports of the relationship between progressive structural damage in glaucoma and longitudinal change in QoL.

In the present study, we expanded our previous investigation and examined the relationship between longitudinal changes in QoL and the rate of RNFL loss in patients with glaucoma.

**Methods**

This longitudinal observational cohort study consisted of participants from the Diagnostic Innovations in Glaucoma Study (DIGS): Functional Impairment, conducted at the Visual Performance Laboratory, Department of Ophthalmology, University of California, San Diego. Written informed consent was obtained from all participants, and the institutional review board of the University of California, San Diego approved all methods. All methods adhered to the Declaration of Helsinki.

At each visit during follow-up, patients underwent a comprehensive ophthalmologic examination including review of medical history, best-corrected visual acuity, slitlamp biomicroscopy, intraocular pressure, gonioscopy, dilated ophthalmoscopic examination, stereoscopic optic disc photography, spectral-domain optical coherence tomography (SD-OCT) testing (Spectralis SD-OCT; Heidelberg Engineering) and standard automated perimetry (SAP) using the Swedish Interactive Threshold Algorithm (SITA standard 24-2; Carl Zeiss Meditec Inc). Patients were excluded if they had any ocular or systemic disease that could affect the optic nerve or visual field.

All patients had a diagnosis of glaucoma at baseline. Eyes were classified as having glaucoma based on repeatable (\(\geq 3\) consecutive) abnormal SAP results at baseline, defined as a pattern standard deviation with \(P < .05\) and/or had glaucoma hemifield test results outside normal limits. A patient was considered to have glaucoma if visual field loss was present in at least 1 eye.

For inclusion in the analysis, each patient was required to have at least 5 SAP and 5 SD-OCT tests and a minimum of 2 NEI VFQ-25 questionnaires over a follow-up duration of at least 2 years. Each patient performed the NEI VFQ-25 annually, with SAP and SD-OCT obtained at 6-month intervals.

**Optical Coherence Tomography**

The Spectralis SD-OCT (software version 5.4.7.0; Heidelberg Engineering) was used to measure RNFL thickness in the present study. The device has been described in detail previously.\(^19\)\(^,\)\(^20\) All images were reviewed to ensure the scan was centered, with signal strength higher than 15 dB and without artifacts or RNFL segmentation errors.

The SD-OCT RNFL thickness parameter used in the study was the global RNFL thickness corresponding to the average of all measures in the peripapillary circle. To determine a binocularly relevant RNFL thickness measure for each patient, we used the thicker measurement between the 2 eyes at each point during follow-up. We herein denominate this measure as *binocular RNFL thickness*. We avoided using data only from a single eye classified as worse or better based solely on the baseline visit, as performed in previous cross-sectional studies. Because the 2 eyes can progress at different rates over time, the better eye at baseline would not necessarily stay as the better eye during follow-up.

**SAP: Monocular and Binocular Visual Fields**

Monocular visual fields were performed using 24-2 SITA standard and evaluated for reliability and presence of artifacts. Visual fields were excluded if they had more than 33% fixation losses or false-negative errors or more than 15% false-positive errors.

To evaluate BVF loss, sensitivities of the monocular SAP tests of the right and left eyes were combined to calculate an integrated BVF, according to the binocular summation model described by Nelson-Quigg et al.\(^21\) Evaluation of the rates of visual field change was performed using the mean sensitivity (MS) of the BVF. Mean sensitivity was calculated as the average of the BVF threshold sensitivities for each integrated field.

**Demographic, Socioeconomic, and Clinical Variables**

Socioeconomic and clinical questionnaires were also administered to patients at the time of the baseline NEI VFQ-25. Because these variables could potentially affect patient perceptions about QoL, they were included as potential confounding factors.
Table 1. Baseline Clinical and Demographic Characteristics of Patients Included in the Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD) [Range]</th>
<th>Patients With Glaucoma (N = 130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>69 (11) [32 to 95]</td>
<td></td>
</tr>
<tr>
<td>Female, %</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>83 (64)</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>41 (31)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>6 (5)</td>
<td></td>
</tr>
<tr>
<td>LogMAR visual acuity (better eye)</td>
<td>0.01 (0.1) [−0.15 to 0.19]</td>
<td></td>
</tr>
<tr>
<td>Baseline RNFL thickness, μm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worse eye</td>
<td>75.1 (17.0) [42 to 119]</td>
<td></td>
</tr>
<tr>
<td>Better eye</td>
<td>84.4 (15.1) [53 to 120]</td>
<td></td>
</tr>
<tr>
<td>Baseline MD, dB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worse eye</td>
<td>−5.1 (5.3) [−25.8 to 1.8]</td>
<td></td>
</tr>
<tr>
<td>Better eye</td>
<td>−2.1 (3.6) [−25.6 to 2.5]</td>
<td></td>
</tr>
<tr>
<td>Baseline binocular mean sensitivity, dB</td>
<td>28.1 (3.4) [9.1 to 33.5]</td>
<td></td>
</tr>
<tr>
<td>Baseline NEI VFQ-25 Rasch-calibrated score</td>
<td>55.3 (23.3) [0 to 100]</td>
<td></td>
</tr>
<tr>
<td>History of glaucoma-filtering surgery, % yes</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Education level, % with at least high school degree</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>Income, &lt;$25 000, %</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Marital status, % married</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Comorbidity index score</td>
<td>1.4 (1.2) [0 to 4]</td>
<td></td>
</tr>
<tr>
<td>Insurance, % yes</td>
<td>92</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MD, mean deviation from standard automated perimetry; NEI VFQ-25, 25-Item National Eye Institute Visual Function Questionnaire; RNFL, retinal nerve fiber layer.

Table 1 shows the baseline clinical and demographic characteristics of patients included in the study. Mean (SD) age was 69 (11) years. At baseline, mean (SD) mean deviations from SAP of the worse and better eyes (as defined by baseline mean deviation from SAP) were −5.1 (5.3) dB and −2.1 (3.6) dB, respectively. The corresponding mean (SD) RNFL thicknesses for these eyes at baseline were 75.1 (17.0) μm and 84.4 (15.1) μm.

Factors. These questionnaires contained a survey about demographics, history of glaucoma-filtering surgery, ocular and medical conditions, marital status (married [yes/no]), health insurance coverage (yes/no), degree of education (at least high school degree [yes/no]), and income (< $25 000/year [yes/no]). For comorbidities, we investigated the presence or self-reported history of the following conditions: diabetes mellitus, arthritis, high blood pressure, heart disease, stroke, depression, asthma, and cancers. A simple summation score was used to create a comorbidity index.24

Visual acuity was measured during follow-up using an Early Treatment Diabetic Retinopathy chart and logMAR measurements were used in the analyses. Change in visual acuity during follow-up was calculated as the difference between the logMAR visual acuity at the last follow-up visit and baseline visit.

**Rasch Analysis of NEI VFQ-25 Questionnaire Data**

Quality of life was evaluated using the NEI VFQ-25. This questionnaire consists of a set of 25 questions designed to assess the dimensions of self-reported vision-target health status that are relevant for patients with chronic eye diseases.23,24 Rasch analysis was performed to obtain final estimates of person measures or Rasch scores. We previously published the details of the Rasch modeling procedure in this population.8 Rasch scores can be used to express where each respondent falls on a linear scale representing the degree of impairment as measured by the NEI VFQ-25 and can be used for subsequent parametric statistical analyses.25,26 Rasch analysis locates item difficulty and person ability on a logit (log odds) scale. Person ability scores were rescaled linearly to range from 0 to 100. Person and item measures were examined for fit to the Rasch model using infit and outfit item fit statistics, and model fitting has been previously described.8

**Statistical Analyses**

After analyzing the NEI VFQ-25 responses using Rasch models, the association between these scores, SAP and RNFL data, was performed with a joint multivariable longitudinal linear mixed model.27 Details about these models have been discussed previously in the literature.28-30

In this type of analysis, the average evolution of a specific response is described using a linear function of time, and patient-specific deviations from this average evolution are introduced by random intercepts and random slopes, allowing for different baseline values and different rates of change for each patient. In a joint-modeling approach using mixed models, random effects are determined for each response process and the different processes are associated by imposing a joint multivariate distribution on the random effects.31 The joint multivariate mixed model permits one to assess how the longitudinal responses were associated over time, that is, change in QoL, as measured by the NEI VFQ-25 scores, were associated with the rate of RNFL loss and with the rate of SAP loss. Individual slopes were obtained from best linear unbiased prediction.28-30

Multivariable linear regression modeling was used to evaluate the combined effect of structural and functional change in QoL deterioration. For this model, the rates of change in NEI VFQ-25 scores were entered as the dependent variable, whereas the rates of change in RNFL thickness and SAP and baseline disease severity were included as independent variables. An additional model was run using the same variables but also including adjustment for the potential confounding variables of change in visual acuity, age, race/ethnicity, sex, marital status, educational level, income level, health insurance coverage, presence of comorbidities, and history of filtering surgery.

Statistical analyses were performed using commercially available software Winsteps version 3.81.0 and Stata version 13 (StataCorp LP). The α level (type I error) was set at .05.

**Results**

This study included 260 eyes of 130 patients with glaucoma. Table 1 shows the baseline clinical and demographic characteristics of the included patients. Mean (SD) age at baseline was 69 (11) years. At baseline, mean (SD) mean deviations from SAP of the worse and better eyes (as defined by baseline mean deviation from SAP) were −5.1 (5.3) dB and −2.1 (3.6) dB, respectively. The corresponding mean (SD) RNFL thicknesses for these eyes at baseline were 75.1 (17.0) μm and 84.4 (15.1) μm.
Patients were followed up for a mean (SD) of 3.5 (0.7) years, ranging from 2.0 to 4.8 years. Patients answered a median of 3 NEI VFQ-25 questionnaires during follow-up, ranging from 2 to 5. The median numbers of available SAP and SD-OCT tests during follow-up were both 7 (interquartile range, 5-9).

There was a correlation between change in the NEI VFQ-25 scores during follow-up and change in binocular RNFL thickness (Figure 1). Each 1-μm-per-year loss in binocular RNFL thickness corresponded to a change of 0.1 units per year in the NEI VFQ-25 scores ($R^2 = 19\%; P < .001$). There was also an association between change in NEI VFQ-25 scores during follow-up and change in binocular MS in our sample (Figure 2). Each 1 dB per year of change in binocular MS corresponded to a change of 3.2 units per year in the NEI VFQ-25 scores during the follow-up period ($R^2 = 25\%; P < .001$).

Eyes with more severe visual field loss at baseline were more likely to have a decrease in NEI VFQ-25 scores during follow-up. Each 1-dB-lower baseline binocular SAP MS was associated with a 0.26-unit greater decline per year in NEI VFQ-25 scores during follow-up ($R^2 = 17\%; P < .001$). An association between baseline binocular RNFL thickness and change in NEI VFQ-25 scores was not identified ($R^2 = 2\%; P = .08$).

The rate of change in binocular RNFL thickness was still a predictor of change in NEI VFQ-25 scores even after inclusion of the rate of change in binocular SAP MS and baseline SAP MS in a multivariable model (Table 2). In the multivariable model, each 1-μm-per-year loss in binocular RNFL thickness corresponded to a decrease of 1.3 units per year in the NEI VFQ-25 scores ($P < .001$). This multivariable model had an $R^2$ of 59% (95% CI, 47%-72%) in explaining change in NEI VFQ-25 scores in our population. The squared semipartial correlation coefficient for rates of binocular RNFL thickness was 26% (95% CI, 12%-39%). This represents the proportion of the outcome (change in NEI VFQ-25 scores) that was associated uniquely with change in binocular RNFL thickness, after adjusting for the contribution from SAP.

The rate of change in binocular RNFL thickness remained a predictor of change in NEI VFQ-25 scores after adjustment for potential confounding socioeconomic and clinical variables, as shown in Table 2. This full multivariable model had $R^2$ of 63% (95% CI, 52%-74%).

Figure 1. Association Between the Change in 25-Item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) Scores and Change in Retinal Nerve Fiber Layer (RNFL) Thickness

Figure 2. Association Between the Change in 25-Item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) Scores and Change in Binocular Mean Sensitivity

Scatterplot with fitted regression line showing the relationship between the change in NEI VFQ-25 scores and change in binocular RNFL thickness (micrometers/year). The shaded area corresponds to the 95% CIs of the regression slope.

Scatterplot with fitted regression line showing the relationship between the change in NEI VFQ-25 scores and change in standard automated perimetry binocular mean sensitivity (decibels/year). The shaded area corresponds to the 95% CIs of the regression slope.

Discussion

In the present study, progressive glaucomatous structural damage, measured by change in RNFL thickness, was associated with a decrease in QoL over time. There was also an association between change in NEI VFQ-25 scores during follow-up and change in binocular SAP sensitivity; however, the rate of change in binocular RNFL thickness remained associated with NEI VFQ-25 scores even after accounting for visual field loss over time. To our knowledge, this is the first study to describe an association between progressive RNFL loss and changes in QoL in patients with glaucoma.

In the univariable model, each 1-μm-per-year loss in binocular RNFL thickness was associated with a change of 1.1 units per year in the NEI VFQ-25 scores. Importantly, change in binocular RNFL thickness was still associated with change in QoL even after adjustment for baseline visual field damage and rates of binocular MS, as measured by standard perimetry. In the multivariable model, each 1-μm-per-year loss in binocular RNFL thickness was associated with a change of 1.3 units per year in the NEI VFQ-25 scores. To better qualify these amounts...
of change, it is important to note that the Rasch scores varied from 0 to 100, from the worst (0) to the best (100) reported QoL in the sample. Therefore, a loss of 8 μm of binocular RNFL would be associated with a 10-point loss or about 10% of the range of Rasch scores in our sample. Importantly, the change in binocular RNFL thickness corresponded to the change seen when using the thickest measurements between the 2 eyes of the same patient over time. Therefore, substantial loss of RNFL had to occur in the better eye or in both eyes to produce meaningful changes in QoL.

Even after the contribution of baseline visual field damage and rates of visual field loss were taken into account, changes in binocular RNFL thickness still explained 26% of the variability in change in NEI VFQ-25 scores. This is an important finding because it demonstrates that assessment of structural damage provides additional information for predicting change in QoL besides what can be gathered by assessment with standard perimetry. This may have several explanations. It is possible that SAP may not fully capture the changes in vision that are relevant to QoL. Standard automated perimetry assesses functional loss by using static white-on-white stimulus presentation, which may fail to capture deficits in other aspects of vision that may be relevant to QoL such as motion perception. Previous research has also indicated that significant neural losses may occur in the macular area of patients with glaucoma. These macular losses are likely to be relevant to several domains of QoL, however, they are usually not detectable by the conventional 24-2 pattern of visual field testing, which evaluates only a very small number of points in this region. On the other hand, previous studies have shown that these neural losses are generally detectable by measurements of RNFL thickness. Additionally, SAP test-retest variability may sometimes preclude an accurate and precise assessment of glaucomatous progression over time, decreasing the association with change in QoL. The use of an additional test measuring progression could improve the assessment of longitudinal damage from the disease. There is evidence demonstrating that patients with glaucoma sometimes show progression based only on structural tests but not functional tests and vice versa. Additionally, the use of combined approaches incorporating functional and structural tests has been shown to provide better assessment of progression than the isolated use of these tests.

Our findings are in agreement with a previous cross-sectional study that evaluated the impact of RNFL damage on functional impairment assessed by the Glaucoma Activity Limitation 9 questionnaire. However, we found a much stronger relationship between structural measurements and QoL. This is probably related to the longitudinal nature of our study. Investigations of this relationship using cross-sectional data are limited by the wide interindividual variability in subjective perceptions about QoL and by possible effects of compensatory mechanisms. In addition, measurement variability may significantly weaken the relationship between the tests. We used joint longitudinal mixed effects modeling to evaluate the association between change in QoL and change in binocular RNFL thickness. By incorporating measurement error, these models provide a better assessment of the true relationship between the longitudinal measures.

The present study had limitations. Although this was a longitudinal study, the follow-up time was relatively short. Despite this, the associations found in the study were relatively strong, statistically significant, and clinically relevant. In our analyses, we assumed linear changes over time in the different variables assessed in the study. However, there is evidence that visual field losses might not follow a linear course over the full course of the disease. Although such
assumption of linearity is probably reasonable within the follow-up times considered in clinical practice, future investigations over longer periods of follow-up should help clarify the full time course of changes in QoL and factors associated with it. It is possible also that the NEI VFQ-25 does not fully capture the whole impact of glaucoma on QoL.40-41 Future studies should investigate the relationship between structural changes and other metrics of QoL and performance-based tests.

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Study concept and design: Tatham, Medeiros.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Gracitelli, Abe, Tatham, Medeiros.
Critical revision of the manuscript for important intellectual content: All authors.
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Study supervision: Gracitelli, Abe, Tatham, Medeiros.
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REFERENCES

Conclusions
Progressive RNFL thickness loss was associated with loss in QoL in patients with glaucoma, even after adjustment for the degree of visual field loss as measured by standard perimetry. These findings provide evidence that the rates of structural change assessed by OCT imaging are valid markers for the degree of self-reported disability associated with glaucoma.
Institute Visual Function Questionnaire (NEI-VFQ).


