Longitudinal Structure-Function Relationships With Scanning Laser Ophthalmoscopy and Standard Achromatic Perimetry

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Objective: To explore longitudinal correlations between structural and functional rates of glaucoma progression with confocal scanning laser ophthalmoscopy and standard achromatic perimetry.

Methods: In this retrospective longitudinal study, 108 eyes with suspected or established glaucoma and 5 or more good-quality scanning laser ophthalmoscopy examinations (global pixel SD <50 µm) and 6 or more reliable visual field (VF) examinations were included. Global and regional rates of progression for VF sensitivity and rim area (RA) were calculated with linear regression analysis. Correlations of global and regional rates of progression were calculated with bivariate correlation analyses. Linear mixed models were built to determine predictive factors for functional and structural changes over time.

Results: The mean (SD) baseline mean deviation was −4.6 (4.9) decibels. The inferotemporal and superotemporal RAs had the highest overall rates of decay (0.0018 mm²/y). Glaucoma progressed in 38 (35.2%) and 20 (18.5%) eyes based on event and trend mean deviation criteria, respectively. The highest correlations of rates were observed between the superonasal or superotemporal RA and inferior VF clusters (r=0.25-0.39; P < .03). Follow-up time, baseline RA, and their interaction were the only significant predictors for RA change; belonging to the group with progression was not associated with higher rates of RA progression.

Conclusions: Longitudinal structure-function relationships are fair at best in eyes with suspected or established glaucoma. Eyes with progressing disease according to VF criteria do not show significantly higher rates of RA progression. Both structural and functional outcomes need to be monitored to detect glaucoma progression in a timely manner.

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GLAUCOMA IS CHARACTERIZED by progressive retinal nerve fiber layer (RNFL) and optic nerve head damage, with or without corresponding visual field (VF) loss. Diagnosis and follow-up of patients with glaucoma are based on clinical examination and ancillary tests to detect and stage evidence of structural and functional damage. A better understanding of the relationship between structural and functional changes over time would help clinicians better measure and predict the rates of disease progression. Structural and functional damage in glaucoma are driven by the loss of retinal ganglion cells and their axons. The strength of cross-sectional structure-function relationships has been found to be fairly weak except in advanced glaucoma. Concordance of signs of structural and functional progression would confirm clinical suspicion for change and reduce the need for multiple confirmations of glaucoma progression. In fact, a unified structure-function model would have considerable clinical implications for intertest confirmation of detection of glaucoma and its progression. Also, if longitudinal structure-function relationships were adequately strong, structural changes could be used as a proxy for subsequent VF change.

There are limited data in the literature regarding longitudinal concordance of structural and functional changes in glaucoma. Because detection of change as an event is artificial and highly dependent on the metric used for detection of change, correspondence of rates and direction of change are important issues that need to be explored. Medeiros et al reported that eyes with clinically progressing glaucoma demonstrated worse rates of change of RNFL thickness measured by scanning laser polarimetry with variable corneal compensa-
tion compared with clinically stable eyes. Alencar et al reported similar findings with regard to RNFL measurement with optical coherence tomography, but the change in rim area (RA) was not significantly different in the groups with or without progression. This lack of complete concordance is a well-known phenomenon in cross-sectional studies and is expected to some extent when longitudinal rates of change are explored.

In this longitudinal study, we investigated the correlation between global and sectoral rates of progression of neuroretinal RA derived from scanning laser ophthalmoscopy (Heidelberg Retina Tomograph 3 [HRT]; Heidelberg Engineering) and global and regional rates of VF decay in a group of patients with suspected or early glaucoma.

**METHODS**

**PARTICIPANTS**

In this retrospective, longitudinal, observational study, 108 eyes (72 patients) with suspected or established glaucoma from Jules Stein Eye Institute’s clinical database who met predetermined inclusion criteria were recruited. The institutional review board at UCLA approved the study, and the tenets of the Declaration of Helsinki were followed. Inclusion criteria were as follows: age older than 30 years, baseline best-corrected visual acuity 20/100 or better, follow-up time 5 or more years, spherical equivalent more than −8 diopeters and astigmatism less than 3 diopeters, 5 or more available HRT examinations with global pixel standard deviation less than 50 µm, and 6 or more reliable standard achromatic VF examinations. The intervals between the first and last VF and HRT examinations were within 6 months. The intraocular pressure (IOP) was required to be more than 8 mm Hg at the time of each HRT examination. Eyes with significant retinal or neurologic diseases were excluded.

Eyes with at least 2 consecutive, reliable abnormal VF test results at baseline (defined as a pattern standard deviation with \( P < .05 \)) and/or glaucoma hemifield test results outside normal limits were classified as glaucomatous regardless of the appearance of the optic disc. Eyes with suspected glaucoma had suspicious or glaucomatous-looking optic discs and/or elevated IOP (>21 mm Hg) with normal VF results at baseline. If both eyes of the same patient were eligible for the study, both were included in the analyses. During follow-up, each patient was treated at the discretion of the attending ophthalmologist. Baseline demographic and clinical data were abstracted from the charts as follows: age, sex, race, best-corrected visual acuity, refractive error, lens status, Goldmann IOP measurements, and number of medications.

Standard achromatic perimetry (24-2 full threshold or SITA [Swedish Interactive Thresholding Algorithm] standard) VF tests were exported to a personal computer using commercial software (PeriData Software GmbH). Visual field reliability criteria for inclusion in the study were fixation loss and false-positive and false-negative response rates of 33% or less. Average threshold sensitivities in VF clusters defined by Garway-Heath et al were calculated in decibel (dB) units after conversion to threshold sensitivities in VF clusters defined by Garway-Heath et al. Positive and false-negative response rates of 33% or less. Average regional correlation is a well-known phenomenon in cross-sectional studies and is expected to some extent when longitudinal rates of change are explored.

In this longitudinal study, we investigated the correlation between global and sectoral rates of progression of neuroretinal RA derived from scanning laser ophthalmoscopy (Heidelberg Retina Tomograph 3 [HRT]; Heidelberg Engineering) and global and regional rates of VF decay in a group of patients with suspected or early glaucoma.

**STATISTICAL ANALYSIS**

Visual field MD and the average sensitivity in VF clusters were regressed against follow-up time to estimate rates of functional progression using ordinary linear-squares methods. Similarly,
regardless of the statistical significance. This way, true correlation to eyes showing a negative trend on structural trend analyses, relation analyses of structural and functional rates of progressing or driving functional change, we limited the bivariate correlation analyses of structural and functional rates of progressing to assuming that structural change is the event preceding or driving functional change, we limited the bivariate correlation analyses of structural and functional rates of progressing to eyes showing a negative trend on structural trend analyses, regardless of the statistical significance. This way, true correlations would be less likely to go undetected because of the noise potentially introduced by stable eyes. Linear mixed models (LMMs) were used to simultaneously assess factors that affect global and sectoral rim area change. The general model used for both global and sectoral change is of the following form: RA change over time = a (follow-up time) + b (baseline RA) + c (VF status) + d (interaction) + random eye effect + random error. Visual field status was coded as progressing (1) or stable (0). Analyses were carried out where the follow-up time × VF status interaction, the follow-up time × baseline RA interaction, or both were evaluated, and random slopes and intercepts were allowed. A total of 7 variations of this model were considered, with and without interactions for global and regional outcomes. The regression coefficients derived from the LMM (representing slopes of change over time) represent the mean slope across all eyes. The inclusion of random eye effects takes into account the nonindependence of the 2 eyes from the same patient. A second series of LMMs was constructed to detect factors predictive of rates of VF change. Specifically, rates of structural change were the main predictors, adjusting for other possible baseline confounding factors. Because the number of HRT examinations was generally less than that of VFs, interpolated values were computed separately for global and sectoral HRT RAs for each eye, using spline regression on follow-up time, accounting for trends over time. The α level (type I error) was set at .01 given the multiple analyses performed.

A total of 72 patients (108 eyes) were enrolled. The mean (SD) follow-up times were 9.4 (3.8) and 8.9 (2.8) years for HRT and VF examinations, respectively. The mean numbers of available HRT and VF examinations were 5.6 (0.8) and 13.0 (5.7), respectively. The baseline and demographic characteristics of the study sample are summarized in Table 1 and Table 2. The mean baseline MD was 1.2 (0.15 to 1.11). Figure 2 shows the distribution of rates of change for global RA and MD in the entire study sample. The inferotemporal and superotemporal RAs demonstrated the highest sectoral rates of decay (0.0018 mm/y). As can be observed in Figure 2, the overall rates of change were fairly small. Glaucoma in 38 (35.2%) and...
20 (18.5%) eyes progressed based on the event and trend MD criteria, respectively.

Global and regional structural and functional rates of progression were weakly correlated in eyes demonstrating a worsening trend on HRT (Table 3 and Figure 3). The highest correlations were observed between the supronasal RA and inferotemporal or inferonasal VF clusters (Spearman $\rho = 0.39$ and 0.32; $P = .001$ and $P = .009$, respectively) and the superotemporal RA and the inferotemporal VF cluster (Spearman $\rho = 0.32$; $P = .004$) (Table 3 and Figure 3). We explored the influence of baseline global and sectoral RA on structural rates of progression. A larger baseline RA was associated with worse (more negative) rates of progression globally and in sectors with the association varying from $-0.30$ (Pearson $r$; $P = .002$) in the superotemporal sector to $-0.54$ in the temporal sector ($P < .001$).

Separate LMMs were explored for change of global and sectoral RAs (7 total regression analyses). In all regression models, follow-up time and baseline RA and their interaction were the only statistically significant predictors for structural change, whereas belonging to the group with progression according to either VF criteria was not associated with significantly worse rates of structural progression ($P = .05-.89$ for the MD trend analysis and $P = .05-.79$ for MD event analyses) (Figure 4). A second series of LMMs (7 separate regressions for global and regional VF measurements over time as the dependent variable) was constructed to explore whether changes from baseline in RA predicted changes in VF sensitivity from baseline. With the change in VF MD or average cluster sensitivity as the main outcomes, baseline MD or average threshold was the main statistically significant predictor of functional change ($P \leq .05$) for MD, supronasal, superotemporal, and inferonasal clusters. Changes in RA in each sector did not predict changes of the corresponding VF cluster ($P = .31-.47$), except for the supronasal VF cluster (predicted by change in the inferonasal sector; $P = .045$) and the temporal cluster (predicted by nasal rim) where the regression coefficient was in the wrong direction ($\beta = -6.1; P = .005$). In the LMM, where change in MD was the main outcome, baseline MD approached statistical significance in addition to follow-up time (Table 4) ($P = .04$ and $P < .001$, respectively).

### Table 3. Correlation of Global and Regional Structural and Functional Rates of Progression

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Eyes</th>
<th>Spearman Correlation</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global RA vs mean deviation</td>
<td>67</td>
<td>0.14</td>
<td>.20</td>
</tr>
<tr>
<td>Superior RA vs inferior hemifield</td>
<td>80</td>
<td>0.30</td>
<td>.007</td>
</tr>
<tr>
<td>Inferior RA vs superior hemifield</td>
<td>75</td>
<td>0.09</td>
<td>.46</td>
</tr>
<tr>
<td>Temporal RA vs central VF cluster</td>
<td>55</td>
<td>0.12</td>
<td>.37</td>
</tr>
<tr>
<td>Nasal RA vs temporal VF cluster</td>
<td>49</td>
<td>0.23</td>
<td>.12</td>
</tr>
<tr>
<td>Superotemporal RA vs inferior temporal VF cluster</td>
<td>80</td>
<td>0.32</td>
<td>.004</td>
</tr>
<tr>
<td>Superotemporal RA vs inferior nasal VF cluster</td>
<td>80</td>
<td>0.25</td>
<td>.03</td>
</tr>
<tr>
<td>Superonasal RA vs inferior nasal VF cluster</td>
<td>68</td>
<td>0.32</td>
<td>.009</td>
</tr>
<tr>
<td>Superonasal RA vs inferior temporal VF cluster</td>
<td>68</td>
<td>0.39</td>
<td>.001</td>
</tr>
<tr>
<td>Inferotemporal RA vs superior temporal VF cluster</td>
<td>73</td>
<td>0.11</td>
<td>.37</td>
</tr>
<tr>
<td>Inferotemporal RA vs superior nasal VF cluster</td>
<td>73</td>
<td>-0.07</td>
<td>.58</td>
</tr>
<tr>
<td>Inferonasal RA vs superior temporal VF cluster</td>
<td>59</td>
<td>0.09</td>
<td>.51</td>
</tr>
<tr>
<td>Inferonasal RA vs superior nasal VF cluster</td>
<td>59</td>
<td>0.12</td>
<td>.38</td>
</tr>
</tbody>
</table>

**Abbreviations:** RA, rim area; VF, visual field.

*Each comparison is based on only the eyes demonstrating a negative rim area slope, regardless of $P$ value.*

*Boldface type indicates statistically significant findings.*

In this retrospective longitudinal study, the inferotemporal and superotemporal HRT RAs demonstrated the highest overall rates of decay (0.0018 mm²/y). We found that the main predictive factors for global or sectoral rim decay were a larger baseline RA, longer follow-up time, and their interaction. Specifically, eyes with larger baseline RA tended to show faster rates of rim decay (Figure 4). Overall, the rates of progression were small despite the long available follow-up data. This is likely related to the
fact that our study sample consisted mainly of eyes with suspected glaucoma or eyes with early glaucomatous damage (mean MD, −4.6 dB). In addition, we found that bivariate correlations between functional and structural rates of progression were fairly low at best regardless of statistical significance. Additionally, rates of structural change according to HRT were not significantly different in stable glaucomatous eyes compared with eyes in which glaucoma progressed according to VF criteria. Because the eyes showing progression according to VF criteria did not have a different slope compared with eyes with no signs of VF progression, we conclude that rates of progression were not significantly different between the groups (Figure 4). This was confirmed with LMMs in which most changes in global or regional VF sensitivities over time were not related to changes in RA.

Our results are consistent with those of Alencar et al,6 who reported that there was no significant difference in global and sectoral RA slopes between eyes with stable and progressing glaucoma defined according to VF and clinical optic disc criteria. The estimated rate of decline in global RA found in our study was similar between eyes with progressing and stable glaucoma (approximately −0.006 mm²/y) and was lower than that reported by Poli et al12 (−0.012 mm²/y) but higher than that reported by Kraft and coworkers13 (−0.003 mm²/y). However, the patient population in the study by Poli et al was different from ours, since they included 31 patients with ocular hypertension in whom repeatable VF defects developed during the follow-up. On the other hand, the rates of RA progression in our study are similar to the rates of change reported by Alencar and colleagues6 (−0.006 and −0.007 mm²/y in eyes with stable and progressing disease, respectively). Similar to the study by Alencar et al, with median MD of −3.3 dB in eyes with glaucoma, our study consisted of patients with both suspected and definite glaucoma.

We found a weak association between structural and functional rates of progression. For exploring the association between structural and functional change, we included only eyes showing a negative rim slope. Including all eyes for the bivariate correlation analyses would have introduced a significant amount of noise into the
analyses and would have decreased the magnitude of any potential correlations. This is based on the assumption that structural change precedes functional change. One might, however, argue that functional change can occur before structural change. Therefore, the weak positive correlations found should be considered optimistic estimates. Only 38 and 20 eyes showed disease progression according to our VF progression criteria (MD event and trend criteria, respectively); therefore, our study sample represents a fairly stable group of patients with suspected or early glaucoma. The main significant correlations were between rates of change in the superonasal, superotemporal, and inferotemporal HRT sectors and the corresponding VF clusters, with the highest correlation observed between the superonasal RA slope and the inferotemporal VF cluster (Spearman \( \rho = 0.39; P = .001 \)).

Previously, several cross-sectional studies have investigated the structure-function relationships in glaucoma with different generations of HRT. In the studies described herein, the most defective neuroretinal RAs (inferior sectors) were associated with the VF region most frequently demonstrating VF defects (superior hemifield). Bowd et al reported a significant correlation between superior and inferior HRT sectoral RAs and corresponding regional VF sensitivities. The strongest correlation was observed between the inferotemporal HRT RA and the superonasal VF cluster (linear \( r = 0.16 \); logarithmic \( r = 0.25 \)). In another cross-sectional study, Danesh-Meyer et al found that the strongest correlations were between the superonasal HRT RA and inferonasal VF cluster \( (r = 0.46) \) and the inferotemporal RA with superonasal VF cluster \( (r = 0.46) \). The longitudinal structure-function correlations found in our study were consistent from an anatomic point of view with the reported cross-sectional correlations in studies using HRT and standard achromatic VFs.

Glaucomatous damage can appear earlier on structural or functional tests, depending on the criteria used and the overall reproducibility and variability of the outcome measures used. It is widely accepted that structural changes frequently predate functional change in a large proportion of patients with glaucoma. Also, a few longitudinal studies in patients with suspected glaucoma have shown that development of glaucoma could be detected earlier with imaging techniques than with functional tests. Therefore, there may be a variable lag time between structural and functional changes in any given eye, although this needs to be studied further. The structure-function relationships may also vary at different stages of the disease and depend on the specific structural and functional measures, the statistical model used, and possibly the magnitude of change. For example, Falsini et al did not find evidence of structure-function relationships when using pattern electroretinogram and optical coherence tomography in a group of patients with ocular hypertension.

Our findings and those of cross-sectional studies suggest the need to better characterize structure-function relationships, taking into account a possible temporal lag model between structural and functional measures. Harwerth et al have suggested that, based on evidence from primates with experimental glaucoma, the ideal descriptor of the structure-function relationships could vary at different levels of neural loss. The lack of a solid and parallel longitudinal correlation between structural and functional measures is not therefore unexpected. In fact, because of the redundancy in the number of ganglion cells, some earlier structural changes may not be accompanied by simultaneous functional change. It is only after this reserve is exhausted that a more consistent correlation may be observed. Again, in more advanced stages of glaucoma, detection of a structural change becomes elusive while, frequently, functional outcomes remain the main indicators that are monitored to detect glaucoma progression. Hence, a mismatch in structure-function relationships would again be expected. Superimposed onto this is the measurement variability of functional and structural measurements. In addition, the role of changing medical or surgical treatment of glaucoma on such potential lags needs to be further clarified. For example, if aggressive glaucoma treatment were implemented after a change in the optic disc in an individual eye is observed, the appearance of functional progression could be slowed or prevented.

As discussed herein, the structure-function relationships can also be influenced by the specific structural or functional tests used. Several studies have shown a stronger structure-function association and a higher diagnostic sensitivity for glaucoma detection with RNFL thickness measurements from optical coherence tomography compared with HRT. Alencar et al compared RA measured by HRT, RNFL loss measured by scanning laser polarimetry with variable corneal compensation was more significantly related to glaucoma progression as detected by standard clinical methods (ie, standard achromatic perimetry and/or stereoscopic photographs). In a group of 108 eyes with glaucoma, Leung et al recently noted poor agreement of progression detection among RNFL, neuroretinal RA, and VF measurements. Until we are able to measure the number of remaining retinal ganglion cells and more accurately examine the functional performance of the visual system in each eye, the use of surrogates would never be expected to perfectly capture structure-function relationships.

Several factors have been reported to influence the measurement variability of neuroretinal RA. Intraocular pressure changes due to treatment can affect the ability of RA measurements to detect change over time and limit the application of HRT for monitoring glaucoma progression. We excluded eyes with an IOP of 8 mm Hg or less to minimize this confounding effect. Another potential source of variability is the instability of the reference plane height used to calculate RA. Variations of the reference plane height have been shown to be associated with variation of RA measurements.

In the LMM for structural trends, we found that longer follow-up time and larger baseline global RA and their interaction were the most significant predictors for worsening of global or sectoral RA. This is likely a floor effect. In eyes with smaller RA at the onset of follow-up, there is less room for change over time. Also, the variability of measurements potentially increases as the RA decreases. Linear mixed models with longitudinal changes in global (MD) or regional VF sensitivity as the main outcome showed a longer duration of follow-up to be the main significant predictor for change in functional measure.
line RA nor changes in global or sectoral RA were associated with functional changes over time, except for a possible trend seen between the superonasal sector RA and inferotemporal cluster. This confirmed our findings from the first series of LMMs, in which the change in RA was the main outcome.

The shortcomings of our study need to be considered. Our study mostly consisted of eyes with suspected or mild glaucoma. Therefore, our results cannot be generalized to eyes at different stages of glaucoma. Also, given the retrospective design of the study, there were a limited number of HRT images and VF examinations available. The precision of slopes (or rates) of change is limited when linear regression is performed on a fairly small number of points during follow-up. The long follow-up of eyes included in this study was also a likely cause for lower rates of progression seen in our sample, since any amount of progression observed was assumed to have happened at a steady rate during the period of follow-up. We did not average the baseline fields or require confirmation of change at the end of follow-up for MD event analyses given the relatively small number of available VFs during the long available follow-up period. This may have increased the false-positive rate for detection of VF progression with MD event analyses and hence led to lower correlation of longitudinal structural and functional measures in LMMs. However, given the fact that the results from MD event analyses were similar to those from trend analyses, we do not believe that the bias introduced is clinically significant.

In conclusion, we found that longitudinal structure-function relationships as measured with HRT and achromatic VFs were fair at best. Evaluation of both structural and functional measures over time is needed for timely detection of change in glaucoma. The main determinant of progressive rim loss on HRT was the magnitude of RA at baseline, with larger RA at baseline predicting higher structural progression rates. Eyes with progressing glaucoma according to global VF criteria did not show significantly higher rates of structural progression in our study.

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REFERENCES


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