The Fast Component of Visual Field Decay Rate Correlates With Disc Rim Area Change Throughout the Entire Range of Glaucomatous Damage

Ji-Woong Lee,1,2 Eun-Ah Kim,1 Francisco Otarola,1 Esteban Morales,1 Fei Yu,1,3 Abdelmonem A. Afifi,3 Kouros Nouri-Mahdavi,1 and Joseph Caprioli1

1The Jules Stein Eye Institute, David Geffen School of Medicine at University of California, Los Angeles (UCLA), Los Angeles, California, United States
2Department of Ophthalmology, Pusan National University School of Medicine, Busan, South Korea
3Department of Biostatistics, Jonathan and Karin Fielding School of Public Health at UCLA, Los Angeles, California, United States

PURPOSE. We investigated the longitudinal relationships between the changes in neuroretinal rim area (RA) and the slow (SC) and fast (FC) components of visual field (VF) decay at various stages of glaucoma.

METHODS. We divided 465 eyes of 338 patients into glaucoma suspect, and preperimetric, early, and moderate/advanced glaucoma. All patients had a minimum of 3 confocal scanning laser ophthalmoscopic examinations and 4 VF tests with follow-up of 4 or more years. A pointwise exponential regression was used to perform trend analyses on thresholds at each VF test location, which was partitioned into SC and FC. A mixed effects linear model was used to explore the associations of RA change with mean deviation (MD), visual field index (VFI), SC, and FC.

RESULTS. Decreased RA was associated with lower mean threshold sensitivities of FC regardless of baseline severity of glaucoma (P \textless 0.03). The mean threshold sensitivities in SC were not correlated with RA change at any stage. Decreased RA was correlated with worse MD in preperimetric, early, and moderate/advanced glaucoma (P \textless 0.05). Decreased RA was correlated with worse VFI in preperimetric and early glaucoma only (P \textless 0.04).

CONCLUSIONS. A decrease in rim area was significantly correlated with the fast VF component regardless of the baseline severity of glaucoma. Mean deviation and VFI correlated with change of rim area only in certain stages of glaucoma. The identification of the fast component seems a more robust and useful measure of glaucomatous change than MD or VFI.

Keywords: fast visual field component, neuroretinal rim area, glaucoma severity

Glaucoma is characterized by progressive optic disc and visual field abnormalities.1 Estimating the rates of structural and functional loss is fundamental to the long-term goal of preservation of vision in patients with glaucoma.2 A better understanding of the precise relationships between structural and functional changes over time would help clinicians better measure and predict the rate of glaucoma worsening.3

Discordance between structural and functional measures should be expected in patients with glaucoma.1,4,5 Many patients may show evidence of optic disc damage before functional loss is detected by standard automated perimetry.6–11 However, some patients may show evidence of visual field change first without clinically apparent optic disc abnormalities.5 Previous studies found a severity-dependent association between structure and function in patients with glaucoma.8–12,16

Few longitudinal studies have evaluated the nature of the structural and functional rates of change in patients with glaucoma as a function of glaucoma severity.17,18 While numerous cross-sectional studies have reported on statistically proven correlations between structure and function,19–21 the use of cross-sectional data to estimate longitudinal behavior in individual patients is not the best approach.1 A technique based on trend analysis that uses a pointwise exponential model to fit the behavior of individual test locations in visual field series has been reported, and separates a slow component (SC) and a fast component (FC) of visual field decay for each eye, and operates successfully across a wide range of disease severity.22–24

The purpose of the present study was to investigate the longitudinal relationships between change in global rim area (RA) as measured with confocal scanning laser ophthalmoscopy (CSLO) with the SC and FC of visual field decay in patients at different stages of glaucoma severity, and to compare these against the standard visual field indices mean deviation (MD) and visual field index (VFI).

METHODS

Participants
In this retrospective, longitudinal, observational study, patients with suspected or established open-angle glaucoma from the Jules Stein Eye Institute’s clinical database were included. This study was conducted in accord with the tenets set forth in the
Declaration of Helsinki and was approved by the UCLA Institutional Review Board. The institutional review board waived consent from patients because this is a retrospective, anonymous study. Inclusion criteria were as follows: age > 30 years, baseline best-corrected visual acuity ≥ 20/80 or better, follow-up time ≥ 4 years, spherical equivalent ≥ −8 diopters, and astigmatism < 3 diopters, ≥ 3 CSLO (Heidelberg Retina Tomograph II [HRT]; Heidelberg Engineering, Heidelberg, Germany) examinations with global pixel standard deviation less than 40 µm, and ≥ 4 reliable visual field examinations. The intervals between the first and last HRT examinations and visual field examinations were within 6 months. Eyes with neurologic or retinal diseases that can affect the visual field were excluded.

Eyes were classified as having suspected glaucoma if they had a history of elevated IOP (>21 mm Hg) and/or suspicious appearance of optic nerve based on stereoscopic photographs reviewed by 2 experienced graders, but normal and reliable visual field results on at least two baseline visits.25 Disagreements between the two graders were resolved by a third experienced grader. Eyes were classified as having preperimetric glaucoma if they had glaucomatous optic neuropathy without evidence of repeatable glaucomatous visual field defect at baseline.26 Glaucomatous optic neuropathy was defined as having more than a 0.2 cup-to-disc ratio asymmetry between the 2 eyes, neuroretinal rim thinning, notching, or characteristic retinal nerve fiber layer defects indicative of glaucoma.27 Eyes were classified glaucomatous if they had a glaucomatous optic disc and two consecutive abnormal visual field test results on the baseline visits. An abnormal visual field was defined as P < 0.05 for the pattern standard deviation or a Glaucoma Hemifield Test result outside normal limits. Eyes with established glaucoma were further classified as having early (MD ≥ −6 dB) or moderate/advanced (MD < −6 dB) glaucoma.28

Data collected from the medical record were age, sex, ethnicity, comorbidity, lens status, best-corrected visual acuity, history of glaucoma surgery and cataract surgery, and number of glaucoma medications and IOP measurements performed by Goldmann applanation tonometry.

Perimetric Tests

All visual field tests were performed with an automated visual field analyzer (Humphrey Field Analyzer; Carl Zeiss Meditec, Inc., Dublin, CA, USA) with a 24-2 test pattern, size III white stimulus with the Swedish Interactive Threshold Algorithm standard strategy. Adequate reliability was defined as less than 15% fixation losses, less than 15% false-positive rates, and less than 30% false-negative rates. The technique of measuring rates of visual field decay has been reported in detail.22,23 and is summarized here. Rates of visual field decay were calculated using a pointwise exponential regression analysis of threshold sensitivities at 52 test locations, excluding the 2 locations within SC or FC with a pointwise exponential regression analysis of threshold sensitivities at 52 test locations, excluding the 2 locations within SC or FC. The association between the global RA was also analyzed with univariate linear regression analyses against time. Eyes with a significant negative trend (slope ≤ −0.3 and P < 0.05) on regression analysis of MD against time were considered to have progressive visual fields. A MD slope of −0.3 dB/y was chosen as a conservative estimate of cutoff for visual field worsening because a previous study reported that mean MD rate ranged from −0.21 to −0.35 dB/y in patients with glaucoma.30 Also, this rate represents a value that is approximately 10 times the magnitude of change due to age alone, a quantity that has been used in many prior studies.30–34

CSLO Imaging

Confocal scanning laser ophthalmoscopy images were acquired with the HRT II device and analyzed with HRT III software. Three sets of 15° field-of-view scans centered on the optic disc were automatically captured at each acquisition. Subsequently, the three sets were used to create a final composite image for analysis. To construct a single examination, the software aligned a stack of individual scans. Each scan was examined for image quality and if any were outside of acceptable quality indices, the scan was discarded from the image set. The optic disc contour line was drawn on the mean topography image by an experienced observer while viewing stereoscopic photographs of the optic disc. The global and sectoral stereometric parameters generated by the HRT software were exported for further analysis. Previous studies showed that global RA was better correlated with functional indices than other HRT parameters,35 and was significantly associated with the development of primary open-angle glaucoma.36 Therefore, global RA was used as the main HRT parameter in subsequent statistical analyses. The difference of global RA from baseline at each visit (global RA at each visit minus baseline global RA) was the main structural measure that was considered. The global RA was also analyzed with univariate linear regression analyses of these values against time.

Statistical Analysis

All statistical analyses were performed with Stata software version 13.0 (StataCorp, College Station, TX, USA). The normality of numerical data distribution was checked with the Kolmogorov-Smirnov test. Clinical characteristics of the study population were compared with ANOVA or the Kruskal-Wallis test for continuous variables and χ2 test or Fisher’s exact test for categorical variables.

Mixed effects linear regression models of MD, VFI, and mean threshold sensitivities of SC and FC were constructed to
There were no statistically significant differences among study groups for baseline age, sex, eye laterality, lens status, ethnicity, comorbidity, HRT and visual field examination follow-up times, and number of HRT examinations. The number of visual field examinations increased significantly in proportion to the severity of glaucoma ($P < 0.001$, Table 1).

Baseline HRT parameters, including the global RA, were significantly worse in the more advanced glaucoma group ($P < 0.001$, Table 1). The proportion of eyes with evidence of progression based on MD regression analysis and that of eyes that received more than one glaucoma surgery during follow-up significantly increased in association with increasing severity of glaucoma ($P = 0.01$ and $P < 0.001$, respectively, Table 3).

Figure 1 shows the overall distribution of rates of change for global RA, MD, VFI, SC, and FC for the entire study sample. There was a statistically significant difference in the global RA rate among four glaucoma groups ($P = 0.002$), and the early glaucoma group had the worst rate. Mean deviation rate, VFI rate, and FC rate were significantly worse in the more advanced groups ($P = 0.038$, $P < 0.001$, and $P < 0.001$, respectively; Table 4). We examined the effect of baseline global RA on global RA rate of change; a greater baseline global RA was correlated with a faster rate of global RA decay in the entire study sample (Spearman's $r = -0.30$, $P < 0.001$, Fig. 2). Global RA rate was positively correlated with the MD rate, VFI rate, and FC rate in the overall group (Spearman's $r = 0.15$, 0.15, and 0.14, respectively; $P = 0.001$, 0.002, and 0.002, respectively), while global RA rate was not correlated with SC rate (Spearman's $r = 0.048$; $P = 0.30$).

With the mixed effects linear regression model, we explored the association between structural change (global RA at each visit minus baseline global RA) and longitudinal measurements of functional parameters (MD, VFI, mean rate, and FC rate). We included 465 eyes of 338 patients in the study. Among the 465 eyes, 88 eyes were classified as glaucoma suspect, 128 eyes as moderate/advanced glaucoma, 147 eyes as early glaucoma, and 102 eyes as preperimetric glaucoma.

The mean (SD) follow-up times of the total study samples were 6.54 (2.13) and 6.64 (2.14) years for HRT and visual field examinations, respectively, while global RA rate was not correlated with SC rate (Spearman's $r = 0.048$; $P = 0.30$).

We included 465 eyes of 338 patients in the study. Among the 465 eyes, 88 eyes were classified as glaucoma suspect, 128 eyes as preperimetric glaucoma, 147 eyes as early glaucoma, and 102 eyes as moderate/advanced glaucoma.

The mean (SD) follow-up times of the total study samples were 6.54 (2.13) and 6.64 (2.14) years for HRT and visual field examinations, respectively, while global RA rate was not correlated with SC rate (Spearman's $r = 0.048$; $P = 0.30$).

We included 465 eyes of 338 patients in the study. Among the 465 eyes, 88 eyes were classified as glaucoma suspect, 128 eyes as preperimetric glaucoma, 147 eyes as early glaucoma, and 102 eyes as moderate/advanced glaucoma. The mean (SD) follow-up times of the total study samples were 6.54 (2.13) and 6.64 (2.14) years for HRT and visual field examinations, respectively, while global RA rate was not correlated with SC rate (Spearman's $r = 0.048$; $P = 0.30$).

We included 465 eyes of 338 patients in the study. Among the 465 eyes, 88 eyes were classified as glaucoma suspect, 128 eyes as preperimetric glaucoma, 147 eyes as early glaucoma, and 102 eyes as moderate/advanced glaucoma. The mean (SD) follow-up times of the total study samples were 6.54 (2.13) and 6.64 (2.14) years for HRT and visual field examinations, respectively, while global RA rate was not correlated with SC rate (Spearman's $r = 0.048$; $P = 0.30$).

We included 465 eyes of 338 patients in the study. Among the 465 eyes, 88 eyes were classified as glaucoma suspect, 128 eyes as preperimetric glaucoma, 147 eyes as early glaucoma, and 102 eyes as moderate/advanced glaucoma.

The mean (SD) follow-up times of the total study samples were 6.54 (2.13) and 6.64 (2.14) years for HRT and visual field examinations, respectively, while global RA rate was not correlated with SC rate (Spearman's $r = 0.048$; $P = 0.30$).

We included 465 eyes of 338 patients in the study. Among the 465 eyes, 88 eyes were classified as glaucoma suspect, 128 eyes as preperimetric glaucoma, 147 eyes as early glaucoma, and 102 eyes as moderate/advanced glaucoma. The mean (SD) follow-up times of the total study samples were 6.54 (2.13) and 6.64 (2.14) years for HRT and visual field examinations, respectively, while global RA rate was not correlated with SC rate (Spearman's $r = 0.048$; $P = 0.30$).

We included 465 eyes of 338 patients in the study. Among the 465 eyes, 88 eyes were classified as glaucoma suspect, 128 eyes as preperimetric glaucoma, 147 eyes as early glaucoma, and 102 eyes as moderate/advanced glaucoma. The mean (SD) follow-up times of the total study samples were 6.54 (2.13) and 6.64 (2.14) years for HRT and visual field examinations, respectively, while global RA rate was not correlated with SC rate (Spearman's $r = 0.048$; $P = 0.30$).

We included 465 eyes of 338 patients in the study. Among the 465 eyes, 88 eyes were classified as glaucoma suspect, 128 eyes as preperimetric glaucoma, 147 eyes as early glaucoma, and 102 eyes as moderate/advanced glaucoma. The mean (SD) follow-up times of the total study samples were 6.54 (2.13) and 6.64 (2.14) years for HRT and visual field examinations, respectively, while global RA rate was not correlated with SC rate (Spearman's $r = 0.048$; $P = 0.30$).

We included 465 eyes of 338 patients in the study. Among the 465 eyes, 88 eyes were classified as glaucoma suspect, 128 eyes as preperimetric glaucoma, 147 eyes as early glaucoma, and 102 eyes as moderate/advanced glaucoma. The mean (SD) follow-up times of the total study samples were 6.54 (2.13) and 6.64 (2.14) years for HRT and visual field examinations, respectively, while global RA rate was not correlated with SC rate (Spearman's $r = 0.048$; $P = 0.30$).

We included 465 eyes of 338 patients in the study. Among the 465 eyes, 88 eyes were classified as glaucoma suspect, 128 eyes as preperimetric glaucoma, 147 eyes as early glaucoma, and 102 eyes as moderate/advanced glaucoma.
Longitudinal Structure–Function Relationship

Table 2. Baseline HRT Stereometric Characteristics of the Study Groups Based on the Diagnosis and Glaucoma Severity of 465 Eyes of 338 Subjects

<table>
<thead>
<tr>
<th>Total, n = 465</th>
<th>GS, n = 88</th>
<th>PPG, n = 128</th>
<th>EG, n = 147</th>
<th>AG, n = 102</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disc area, mm²</td>
<td>2.13 ± 0.46</td>
<td>2.07 ± 0.46</td>
<td>2.11 ± 0.47</td>
<td>2.18 ± 0.46</td>
<td>2.14 ± 0.44</td>
</tr>
<tr>
<td>Cup area, mm²</td>
<td>0.94 ± 0.50</td>
<td>0.71 ± 0.41</td>
<td>0.85 ± 0.45</td>
<td>1.00 ± 0.49</td>
<td>1.18 ± 0.52</td>
</tr>
<tr>
<td>Rim area, mm²</td>
<td>1.19 ± 0.34</td>
<td>1.36 ± 0.26</td>
<td>1.26 ± 0.30</td>
<td>1.18 ± 0.32</td>
<td>0.96 ± 0.35</td>
</tr>
<tr>
<td>Cup/disc area ratio</td>
<td>0.42 ± 0.17</td>
<td>0.32 ± 0.14</td>
<td>0.38 ± 0.15</td>
<td>0.44 ± 0.16</td>
<td>0.54 ± 0.17</td>
</tr>
<tr>
<td>Rim/disc area ratio</td>
<td>0.58 ± 0.17</td>
<td>0.68 ± 0.14</td>
<td>0.62 ± 0.15</td>
<td>0.56 ± 0.16</td>
<td>0.46 ± 0.17</td>
</tr>
<tr>
<td>Cup volume, mm³</td>
<td>0.25 ± 0.21</td>
<td>0.16 ± 0.13</td>
<td>0.22 ± 0.19</td>
<td>0.25 ± 0.20</td>
<td>0.34 ± 0.27</td>
</tr>
<tr>
<td>Rim volume, mm³</td>
<td>0.27 ± 0.14</td>
<td>0.36 ± 0.14</td>
<td>0.29 ± 0.12</td>
<td>0.26 ± 0.13</td>
<td>0.20 ± 0.12</td>
</tr>
<tr>
<td>Mean cup depth, mm</td>
<td>0.29 ± 0.10</td>
<td>0.26 ± 0.09</td>
<td>0.27 ± 0.09</td>
<td>0.29 ± 0.10</td>
<td>0.32 ± 0.12</td>
</tr>
<tr>
<td>Maximum cup depth, mm</td>
<td>0.66 ± 0.19</td>
<td>0.64 ± 0.18</td>
<td>0.67 ± 0.20</td>
<td>0.66 ± 0.18</td>
<td>0.67 ± 0.19</td>
</tr>
<tr>
<td>Height variation contour, mm</td>
<td>0.35 ± 0.12</td>
<td>0.39 ± 0.12</td>
<td>0.35 ± 0.11</td>
<td>0.35 ± 0.11</td>
<td>0.32 ± 0.14</td>
</tr>
<tr>
<td>Cup shape measure</td>
<td>−0.10 ± 0.08</td>
<td>−0.14 ± 0.07</td>
<td>−0.12 ± 0.07</td>
<td>−0.09 ± 0.07</td>
<td>−0.04 ± 0.08</td>
</tr>
<tr>
<td>Mean RNFL thickness, mm</td>
<td>0.20 ± 0.08</td>
<td>0.23 ± 0.08</td>
<td>0.21 ± 0.08</td>
<td>0.20 ± 0.08</td>
<td>0.16 ± 0.08</td>
</tr>
<tr>
<td>RNFL cross-sectional area, mm²</td>
<td>1.02 ± 0.41</td>
<td>1.18 ± 0.42</td>
<td>1.04 ± 0.38</td>
<td>1.03 ± 0.41</td>
<td>0.84 ± 0.37</td>
</tr>
<tr>
<td>Horizontal cup/disc ratio</td>
<td>0.64 ± 0.19</td>
<td>0.56 ± 0.19</td>
<td>0.63 ± 0.18</td>
<td>0.64 ± 0.18</td>
<td>0.71 ± 0.17</td>
</tr>
<tr>
<td>Vertical cup/disc ratio</td>
<td>0.61 ± 0.17</td>
<td>0.50 ± 0.19</td>
<td>0.56 ± 0.16</td>
<td>0.65 ± 0.14</td>
<td>0.73 ± 0.13</td>
</tr>
<tr>
<td>Linear cup/disc ratio</td>
<td>0.63 ± 0.14</td>
<td>0.55 ± 0.13</td>
<td>0.61 ± 0.14</td>
<td>0.65 ± 0.13</td>
<td>0.72 ± 0.13</td>
</tr>
<tr>
<td>Global pixel SD</td>
<td>18.5 ± 7.8</td>
<td>19.5 ± 10.0</td>
<td>18.5 ± 7.8</td>
<td>17.4 ± 6.2</td>
<td>19.3 ± 7.9</td>
</tr>
</tbody>
</table>

RNFL, retinal nerve fiber layer.
* Kruskal-Wallis test.
† Analysis of variance.

Discussions

Threshold sensitivities of SC and FC) after adjusting for baseline age, baseline RA, and follow-up time. The greater decrease in RA was associated with worse MD, VFI, and the mean threshold sensitivities of FC in entire study sample (P < 0.001 for all, Table 5). In the overall group of patients, older baseline age was significantly associated with lower mean sensitivities of FC and SC (P < 0.05 for both). Longer follow-up time was significantly associated with lower MD, VFI, and mean sensitivities of FC (P < 0.001 for all). Smaller baseline global rim area was associated with lower MD, VFI, and mean sensitivities of FC and SC (P < 0.05 for all). In the glaucoma suspect group, only the mean threshold sensitivities of FC correlated with change in RA (P = 0.005). In preperimetric and early glaucoma, decreased RA correlated with worse MD, VFI, and the mean threshold sensitivities of FC (P < 0.05 for all). In moderate/advanced glaucoma, the decreased RA correlated with worse MD and the mean threshold sensitivities of FC (P = 0.046 and P = 0.015, respectively). There was some evidence suggesting that VFI may be associated with structural change in the moderate/advanced glaucoma group even though it did not reach statistical significance (P = 0.075). However, the mean threshold sensitivities of SC were not significantly correlated with change of RA in any of the severity groups or in the entire study sample (P = 0.352–0.878).

Discussion

The objective of this study was to investigate the relationship between global RA decline as measured with CSLO, and the slow and fast visual field components as measured with a pointwise exponential regression model in patients with different baseline glaucoma severities. When we explored the relationship between structural and functional change with a mixed effects linear regression model after adjusting for baseline age and baseline RA, we found that the decline in threshold sensitivities of FC was significantly associated with the decline of RA in all severity groups. The greater decrease in global RA correlated with a worsening of mean threshold sensitivities of FC. The mean threshold sensitivities of SC were not correlated with this structural change in any of the severity groups. Mean deviation was not correlated with RA change in the glaucoma suspect group. Visual field index was correlated with structural change only in preperimetric and early glaucoma.

These findings might be explained by the typically localized characteristic of glaucoma progression.22-25,37 Fast component of visual field decay better characterizes the structure and function relationship over a wide range of glaucoma severities, since it is where we believe most of the glaucoma “signal” resides. It is likely that FC is better associated with structural change than MD or VFI, since we extract and remove the noncorrelating portion (SC) of visual field deterioration.

Shigeeda et al.38 reported that the MD rate of change would be expected to be insensitive to localized components of visual field deterioration. The VFI provides no spatial information about the visual field and seems too insensitive to regional changes or focal components of damage in the same manner.59 Therefore, point-by-point analyses may be more effective in detecting localized components of visual field progression that are closely related with structural change.22-24,39 Mean deviation and VFI may lack sensitivity for detecting early glaucoma progression, because they are global indices that summarize mean damage across the entire visual field.59,60 Alasli et al.15 reported that substantial retinal nerve fiber layer thinning is necessary before MD loss is detected. The reasons for this discordance are likely, because (1) standard automated perimetry may absorb damage without showing abnormalities early on due to the redundancy of visual field sensitivity,41 (2) higher variability is found in the measurements of standard automated perimetry than those of optical coherence tomography in early glaucoma,13 and (3) MD is insensitive to localized low.58 In addition, VFI may be less able to detect early glaucomatous change due to the ceiling effect derived from its reliance on pattern deviation probability maps.59 The fact that VFI is heavily weighted towards the central visual field, which typically is damaged later in disease, perhaps also compromises its ability to detect early glaucomatous change.59

As opposed to the global indices MD and VFI, the method used here enables the identification of the SC and FC components separately, without loss of spatial or pattern information.22-23 Because the FC represents more focal, rapidly deteriorating test locations from glaucoma,22-24 our results suggested that identification of FC may reduce the lag time between clinically detectable structural and functional changes, and enable detection of structure and function relationship.
in glaucoma suspect eyes that are in the early phase of developing glaucomatous damage. In contrast, structural change was not associated with SC at any glaucoma severity, because the SC component reflects more diffuse and nonspecific deterioration, more reflective of media opacity and aging.22–24 While we believe that most of the glaucomatous change resides in the FC component of visual field, it certainly is possible that some slow, relatively diffuse glaucomatous visual field loss resides in SC. Henson et al.42 reported that early glaucomatous visual field loss frequently involves a diffuse component.

In the preperimetric and early glaucoma groups, we found that a greater decrease in global RA was correlated with worse MD, VFI, and the mean threshold sensitivities of FC. Mean deviation and VFI as well as mean threshold sensitivities of FC also were found to be functional parameters that are correlated well with structural changes in preperimetric and early glaucoma groups. It may be that only after redundancy of retinal ganglion cell (RGC) function is exhausted that a strong clinical relationship between structure and function can be detected.18,41 However, Gardiner et al.45 reported that the intertest variability is sufficiently large that the observed discrepancy between the rates of structural and functional change could be a result of noise in early glaucoma. The variability could affect structural as well as functional classification.

Although the mixed effects linear regression model revealed that decreasing RA was associated with worsening MD and the mean threshold sensitivities of FC in the moderate/advanced glaucoma group, a floor effect ultimately will influence the relationship between structure and function in advanced stages of glaucoma. The relationship between structural and functional change also can be influenced by the variability of the measurements,13,45 different measurement scales,44 different statistical methods to estimate change,17 and the particular structural or functional tests used.21,45 Bowd et al.21 reported that global associations between structure and function were stronger with optical coherence tomography than with HRT. Lamparter et al.45 reported that the correlation between structure and function was stronger in flicker defined form perimetry and frequency doubling technology perimetry than with standard automated perimetry. The correlation between structure and function might have been improved with different measurement tests in this study.

There is a residual retinal nerve fiber layer thickness even in patients with severe glaucoma, likely because of displaced amacrine cells and nonneuronal tissues including blood vessels, glial cells.13 Likewise, a proportion of the neuroretinal RA may consist of nonneuronal rim tissue, including blood vessels and glia.46 Nassiri et al.18 reported that a larger baseline RA was associated with a faster rate of progression. We also found that a greater baseline RA was associated with faster rate of decay in RA with the correlation varying from −0.17 (Spearman’s ρ, P = 0.05) in the preperimetric glaucoma group to −0.47 (Spearman’s ρ, P < 0.001) in the moderate/advanced glaucoma group. There might be less room for decay in eyes with a smaller baseline RA, and the variability of RA measurements increases as RA decreases.57 We found that some evidence suggested that VFI may be associated with structural change in the moderate/advanced glaucoma group. However, Lee et al.48 reported that the VFI becomes highly variable in advanced glaucoma, because of the change from the use of the pattern

### Table 3. Changes in IOP, Number of Glaucoma Medications, and Global Visual Field Parameters Among the Study Groups Based on the Diagnosis and Glaucoma Severity of 465 Eyes of 338 Subjects

<table>
<thead>
<tr>
<th></th>
<th>Total, n = 465</th>
<th>GS, n = 89</th>
<th>PPG, n = 127</th>
<th>EG, n = 147</th>
<th>AG, n = 102</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, mean ± SD, mm Hg</td>
<td>15.1 ± 4.5</td>
<td>17.1 ± 4.0</td>
<td>15.7 ± 3.9</td>
<td>14.7 ± 5.0</td>
<td>13.1 ± 4.1</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Follow-up, mean ± SD, mm Hg</td>
<td>14.2 ± 3.1</td>
<td>16.4 ± 3.1</td>
<td>15.1 ± 2.8</td>
<td>13.5 ± 2.7</td>
<td>12.2 ± 2.5</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Fluctuation, mean ± SD, mm Hg</td>
<td>6.5 ± 3.5</td>
<td>5.4 ± 2.6</td>
<td>6.3 ± 5.7</td>
<td>6.5 ± 4.0</td>
<td>6.7 ± 3.3</td>
<td>0.04*</td>
</tr>
<tr>
<td>No. of glaucoma medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, mean ± SD</td>
<td>1.2 ± 1.2</td>
<td>0.43 ± 0.76</td>
<td>1.2 ± 1.1</td>
<td>1.4 ± 1.1</td>
<td>1.6 ± 1.3</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Follow-up, mean ± SD</td>
<td>1.2 ± 1.0</td>
<td>0.42 ± 0.67</td>
<td>1.3 ± 0.9</td>
<td>1.5 ± 0.9</td>
<td>1.5 ± 0.9</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>MD, mean ± SD, dB</td>
<td>−3.7 ± 4.6</td>
<td>−0.2 ± 1.4</td>
<td>−1.1 ± 1.6</td>
<td>−3.0 ± 1.7</td>
<td>−10.8 ± 4.0</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Final</td>
<td>−4.5 ± 5.4</td>
<td>−0.7 ± 2.2</td>
<td>−1.8 ± 3.2</td>
<td>−5.8 ± 2.5</td>
<td>−12.3 ± 5.1</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>PSD, mean ± SD, dB</td>
<td>4.5 ± 3.9</td>
<td>1.7 ± 0.7</td>
<td>1.8 ± 0.6</td>
<td>4.2 ± 2.2</td>
<td>10.6 ± 3.1</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Final</td>
<td>5.2 ± 4.1</td>
<td>2.1 ± 1.9</td>
<td>2.7 ± 2.0</td>
<td>5.2 ± 2.5</td>
<td>11.1 ± 3.0</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>VFI, mean ± SD, dB</td>
<td>91.0 ± 12.4</td>
<td>99.1 ± 12</td>
<td>98.3 ± 1.8</td>
<td>93.1 ± 4.2</td>
<td>71.8 ± 13.0</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Final</td>
<td>87.7 ± 15.8</td>
<td>97.9 ± 4.9</td>
<td>95.9 ± 8.0</td>
<td>90.1 ± 6.9</td>
<td>65.1 ± 16.8</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Eyes with progressing disease based on MD regression criteria, No. (%)</td>
<td>70 (15.1)</td>
<td>4 (4.5)</td>
<td>17 (13.5)</td>
<td>27 (18.4)</td>
<td>22 (21.6)</td>
<td>0.01†</td>
</tr>
<tr>
<td>Eyes that received ≥1 glaucoma surgery during follow-up, No. (%)</td>
<td>49 (10.5)</td>
<td>0 (0)</td>
<td>10 (7.8)</td>
<td>13 (8.8)</td>
<td>26 (25.5)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Eyes requiring more medications ≥ 1 at last visit vs. baseline visit, No. (%)</td>
<td>127 (27.3)</td>
<td>9 (10.1)</td>
<td>35 (27.6)</td>
<td>50 (34.0)</td>
<td>33 (32.4)</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>Eyes that underwent cataract extraction during follow-up, No. (%)</td>
<td>103 (22.2)</td>
<td>9 (10.2)</td>
<td>21 (16.4)</td>
<td>41 (27.9)</td>
<td>32 (31.4)</td>
<td>0.001‡</td>
</tr>
</tbody>
</table>

PSD, pattern standard deviation.
* Kruskal-Wallis test.
† Fisher’s exact test.
‡ χ² test.
FIGURE 1. Distributions of rates of change for global rim area (A), MD (B), VFI (C), SC (D), and FC (E) visual field components in entire study sample.
deviation probability value to the total deviation probability value in calculations of VFI at or below −20 dB of MD. Mean deviation rate, VFI rate, and FC rate were significantly worse in the more advanced groups. Previously, we reported that worse baseline MD was associated with rapid deterioration of visual field loss.49 Chauhan et al.50 also reported that the proportion of fast (MD rate, < −1 to −2 dB/y) and catastrophic (< −2 dB/y) progressors was higher in worst tertile (median baseline MD, −7.79 dB) compared to the other two tertiles. Ernest et al.50 reviewed 85 articles and reported that more baseline visual field loss was probably associated with more visual field progression in patients with open-angle glaucoma.

The estimated rate of global RA change found in our study (−0.018 mm²/y for the entire study sample) was similar to those reported in previous studies (range, −0.013 to −0.015 mm²/y).51,52 The correlations between global RA rate and MD, VFI, and FC rate are all fairly weak in this study. Our results are consistent with previous longitudinal studies that have explored the relationship of structure and function with HRT.17,18 Medeiros et al.17 reported a significant, but weak correlation between slopes of MD and global RA change in our study (Spearman’s $\rho = 0.15; P < 0.001$). Nassiri et al.18 reported that global structural and functional rates of progression were weakly correlated in eyes with suspected or established glaucoma (Spearman’s $\rho = 0.14; P = 0.20$). These findings support previous evidence of low correspondence between structural and functional measures.18,53,54 Differences in the sensitivity–neural relationships for early and advanced visual field defects should be expected. Kerrigan-Baumrind et al.53 reported that at least 25% to 35% RGC loss was associated with statistically significant abnormalities in automated visual field testing in humans. However, Harwerth et al.54 reported that there is a loss of 6 to 8 dB in visual sensitivity over the range of smaller losses of ganglion cells where sensitivity losses appear to be uncorrelated with neural loss in monkeys. They suggested the possibility of an alteration in RGC function before the pathological loss of the cell body. In more advanced glaucoma, functional outcomes often are used to detect glaucoma progression because a structural change becomes difficult to detect.18

The main issue with respect to the relationship between structure and function is whether or not structural changes are clinically relevant to functional outcomes.1 When glaucomatous structural change is suspicious, the clinical evidence of progression might be better corroborated with corresponding changes in FC than with MD or VFI. In addition, FC can be integrated with structural information to improve detection of glaucoma progression in future studies. Caprioli55 reported that the combination of structural and functional measurements performed better than structural or functional measurements alone to discriminate between normal and glaucoma and to detect glaucoma worsening. Medeiros et al.56 reported that a Bayesian hierarchical model for combining longitudinal structural and functional information was more sensitive than ordinary least squares regression in detecting glaucoma progression.

The findings of this study are subject to certain limitations. The sample sizes of the each of the severity subgroups were modest. Given the retrospective and clinical nature of the study, there were a limited number of HRT and visual field examinations available that met our inclusion criteria. The number of usable examinations was determined by an
Longitudinal Structure–Function Relationship

Table 5. Results from Mixed Effects Linear Regression Model for Association Between Structural Change as a Predictor and Functional Change as Each Individual Outcome in Separate Regression Models After Adjusting for Baseline Age, Baseline Global Rim Area, and Follow-Up Time

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>Change in Global Rim Area (Rim Area at Each Visit - Baseline Rim Area), ( \text{mm}^2 )</th>
<th>Total, ( n = 465)</th>
<th>GS, ( n = 88)</th>
<th>PPG, ( n = 128)</th>
<th>EG, ( n = 147)</th>
<th>AG, ( n = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD, dB</td>
<td>( \beta )</td>
<td>1.56</td>
<td>0.34</td>
<td>1.98</td>
<td>1.24</td>
<td>1.61</td>
</tr>
<tr>
<td></td>
<td>( P )</td>
<td>&lt;0.001</td>
<td>0.61</td>
<td>0.002</td>
<td>0.03</td>
<td>0.046</td>
</tr>
<tr>
<td>VFI, %</td>
<td>( \beta )</td>
<td>3.73</td>
<td>&lt;0.001</td>
<td>1.97</td>
<td>5.24</td>
<td>3.53</td>
</tr>
<tr>
<td></td>
<td>( P )</td>
<td>0.11</td>
<td>&lt;0.001</td>
<td>0.11</td>
<td>0.04</td>
<td>4.61</td>
</tr>
<tr>
<td>Mean threshold sensitivities of FC, dB</td>
<td>( \beta )</td>
<td>2.18</td>
<td>&lt;0.001</td>
<td>3.59</td>
<td>1.81</td>
<td>1.19</td>
</tr>
<tr>
<td></td>
<td>( P )</td>
<td>0.003</td>
<td>0.006</td>
<td>0.006</td>
<td>0.03</td>
<td>3.34</td>
</tr>
<tr>
<td>Mean threshold sensitivities of SC, dB</td>
<td>( \beta )</td>
<td>0.19</td>
<td>0.60</td>
<td>-0.20</td>
<td>0.78</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>( P )</td>
<td>0.88</td>
<td>0.35</td>
<td>0.35</td>
<td>0.12</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Decrease in global rim area correlated with worse mean threshold sensitivities of FC visual field component in all severity groups, while the mean threshold sensitivities of SC visual field component were not correlated with the structural change in any of the severity groups.

* Table contains the results for four regression models. The outcome variables are listed in the first column. Each model includes this variable as a covariate. In addition, each model was adjusted for the following covariates: baseline age, baseline global rim area, follow-up time.

† Each column shows the regression results for the total sample as well as the following subgroups: glaucoma suspect, preperimetric glaucoma, early glaucoma, and moderate/advanced glaucoma.

References


