Comparative Study of Retinal Nerve Fiber Layer Measurement by StratusOCT and GDx VCC, II: Structure/Function Regression Analysis in Glaucoma

Christopher Kai-shun Leung,1 Kelvin Kam-Long Chong,2 Wai-man Chan,2 Cedric Ka-Fai Yiu,3 Man-yee Tso,1 Jackson Woo,1 Moon-Kwong Tsang,1 Kwok-kay Tse,1 and Wing-bo Yung4

PURPOSE. To evaluate the structure/function relationship between visual field sensitivity and retinal nerve fiber layer (RNFL) thickness measured by StratusOCT (Carl Zeiss Meditec, Inc., Dublin, CA) and GDx VCC (Laser Diagnostic Technologies, Inc., San Diego, CA).

METHODS. Eighty-nine subjects (27 who had healthy eyes, 21 who were glaucoma suspect, 41 who had glaucoma) were enrolled in this cross-sectional study. RNFL thickness was measured using the StratusOCT and the GDx VCC, and visual field (VF) was examined using the Humphrey VF analyzer. The relationship between RNFL thickness and VF sensitivity—expressed in terms of mean deviation (MD) in decibel (dB) scale, unlogged 1/lambert (L), and Advanced Glaucoma Intervention Study (AGIS) and Collaborative Initial Glaucoma Treatment Study (CIGTS) VF scores—were evaluated with linear and nonlinear regression models. Coefficient of determination ($R^2$) was calculated, and regression models were compared using the Akaike information criterion and the F test.

RESULTS. In plotting MD against RNFL thickness, curvilinear regression models demonstrated the best fit, whereas linear regression attained the best associations when VF sensitivity was expressed in 1/L. However, when healthy subjects were excluded from the analyses, the second-order polynomial was better than linear regression in describing the relation between 1/L and GDx VCC–measured RNFL thickness. Regression profiles between AGIS/CIGTS VF scores and RNFL thickness were best described in the linear and the first-order inverse models for GDx VCC and StratusOCT RNFL measurements, respectively. In general, StratusOCT RNFL measurements achieved higher associations with visual function in all the respective regression analyses than did GDx VCC.

CONCLUSIONS. Description of structure/function relationships in glaucoma depends on the choice of perimeter scale, the type of RNFL measuring device, and the characteristics of the studied groups. The higher association with visual function in StratusOCT RNFL measurements compared with that in GDx VCC suggested optical coherence tomography might be a better approach for evaluating structure/function relationships. Curvilinear regression profiles found between StratusOCT RNFL thickness and MD/VF scores provide an explanation for those longitudinal observations, showing that VFs with higher AGIS/CIGTS VF scores or worse MD at baseline are at higher risk for deterioration. Regression analysis of the structure/function profile could provide important information in the assessment of the trend and pattern of glaucoma progression. (Invest Ophthalmol Vis Sci. 2005;46:3702–3711) DOI: 10.1167/iovs.05-0490

The loss of retinal ganglion cells in glaucoma can be reflected structurally as localized or diffuse thinning of the retinal nerve fiber layer (RNFL), and its measurement has been correlated with the functional damage in visual field (VF).1–4 StratusOCT (Carl Zeiss Meditec, Inc., Dublin, CA) and GDx VCC (Laser Diagnostic Technologies, Inc., San Diego, CA) are the two latest commercially available imaging modalities designed to measure RNFL thickness. A number of recent studies have reported high correlations between VF sensitivity and RNFL thickness in glaucoma with the use of these nerve fiber analyzers. In the study by Reus and Lemi,1 the relationship between VF sensitivity (in decibel [dB]) and GDx VCC RNFL measurements in patients with glaucoma was found with coefficients of correlation of 0.77, 0.52, 0.46, 0.51, and 0.38 at the supratemporal, supranasal, nasal, infranasal, and inferotemporal sectors, respectively. With the use of StratusOCT (Carl Zeiss Meditec), Leung et al.4 showed that the coefficient of correlation between VF mean deviation (MD) and average RNFL thickness was 0.79. Although statistically significant correlations were found in these studies, the structure/function relationship was primarily investigated with linear regression analysis, which may not be an adequate model to describe and fit the nonlinear portion of the relationship. In fact, a curvilinear relationship has been reported between GDx VCC (Laser Diagnostic Technologies)–measured RNFL thickness and VF sensitivity.5 Therefore, comparisons with linear and nonlinear regression models are essential to identify and confirm the precise nature of the structure/function relationship. The regression function would then be useful for understanding the trend and pattern of disease progression and for selecting an appropriate monitoring strategy to detect the changes.

Information regarding the nature of progression in glaucoma has been essentially derived from the longitudinal VF analyses.6–12 To avoid the confounding effect of variability, a number of analytical procedures were suggested to determine the true progression. The Humphrey visual field analyzer (Humphrey Field Analyzer II; Humphrey Instruments, Dublin, CA) has a built-in “change analysis” option that performs linear regression analysis of the VF MD. Major clinical trials such as
the Advanced Glaucoma Intervention Study (AGIS) and the Collaborative Initial Glaucoma Treatment Study (CIGTS) use defect classification scoring systems to provide a discrete score, between 0 and 20, for each VF result.\textsuperscript{13,14} The AGIS and the CIGTS define progression as an increase in VF score of 4 and 3, respectively. However, the scoring systems can be arbitrary, and the scale may not be linear. A change in score from 1 to 5 may not be equal to a change from 16 to 20. Analyzing the structure/function profiles in terms of VF scores may reveal the nature of the scaling of these scoring systems and may provide better understanding regarding the trend of disease progression observed in these trials. Using different nonlinear and linear regression models, we investigated and compared the relationship between VF sensitivity—expressed in terms of decibel units (MD), unlogged (1/Lambert [1/L]), and AGIS/CIGTS VF scores—and RNFL thickness, measured with StratusOCT and GDX VCC, in subjects with glaucoma.

**Materials and Methods**

**Subjects**

One eye was selected randomly from each of 27 healthy subjects, 21 subjects who were glaucoma suspect, and 41 subjects who had glaucoma. All recruited subjects were examined from August to November 2004 in the Department of Ophthalmology, Caritas Medical Centre, Hong Kong. Caritas Medical Centre is the ophthalmic referral center in the Hong Kong Hospital Authority Kowloon West Cluster and serves a population of 1.2 million. The study was conducted in accordance with the ethical standards stated in the 1964 Declaration of Helsinki and was approved by the Hong Kong Hospital Authority Kowloon West Cluster Clinical Research Ethics Committee with informed consent obtained.

All subjects underwent full ophthalmic examination, including visual acuity, refraction, intraocular pressure measurement with Goldmann tonometry, dilated fundus examination with stereoscopic biomicroscopy of optic nerve head under slit-lamp, and indirect ophthalmoscopy. Inclusion criteria were best-corrected visual acuity of not worse than 20/40 and spherical refractive error within the range of −6.00 diopters (D) to +3.00 D. Subjects were excluded if they had history of retinal disease, surgery, laser procedures, diabetes mellitus, or neurologic disease. Healthy subjects visited the clinic during the same recruitment period and had no ocular or intraocular diseases. In particular, they had no VF defects based on the Humphrey VF results, no structural optic disc abnormalities, and no history of intraocular pressure exceeding 21 mm Hg. Glaucoma-suspect subjects were those with ocular hypertension, pre-perimetric glaucoma, or both. Ocular hypertension was defined as intraocular pressure greater than 21 mm Hg measured in at least three separate visits. Pre-perimetric glaucoma was diagnosed when subjects had been found to have asymmetric cup disc ratios of >0.2 and early glaucomatous optic disc changes, including thinning of the neuroretinal rim and notching. However, all subjects in the glaucoma-suspect group had normal VF results, as did the control group with healthy eyes. Glaucoma had been diagnosed in subjects based on the presence of VF defects. Among the 41 patients with glaucoma, 21 had primary open-angle glaucoma, 13 had normal-tension glaucoma, 6 had primary angle-closure glaucoma, and 1 had uveitic glaucoma.

**Visual Sensitivity Measurements**

Visual fields were evaluated with the Humphrey visual field analyzer (central 24-2 STA fast program; Humphrey Instruments). Humphrey VF test results were considered reliable when the fixation loss was <20% and the false-positive and false-negative error rates were <25%. A VF defect was defined as three or more significant (P < 0.05) non-edge-contiguous points, with at least one at the P < 0.01 level on the same side of the horizontal meridian in the pattern deviation plot and classified outside normal limits in the glaucoma hemifield test. Any detected field defect had to be confirmed in at least one other attempt to be classified as abnormal. Average visual sensitivity was expressed in 3 different forms: MD, unlogged 1/L, and AGIS/CIGTS VF scores. MD represents an age-matched average visual sensitivity index expressed in decibels. It is calculated based on the total deviation plot in the Humphrey VF analysis. Differential light sensitivity at each tested location is measured in decibels, where the differential light sensitivity (dB) = 10 × log10 (Imax/Imin), with Imax is the maximal stimulus luminance, I is the stimulus luminance at threshold, and I is the background luminance. For simplicity, this relationship can be written as 10 × log10 (1/L). The unlogged 1/L at each tested location was calculated by dividing the decibel unit by 10 and then unlogging it. The average value was then evaluated. Each VF in the glaucoma group was also analyzed to determine the AGIS/CIGTS VF scores. Both scoring systems use 20-interval scales, with 0 representing no defect and 20 representing severe damage. The scorings of the VFs were computed according to the original descriptions in the respective trials.\textsuperscript{13,14}

**Optical Coherence Tomography Measurements**

StratusOCT (Carl Zeiss Meditec) with software version 3.0.1 was used in the study. Detailed descriptions of the optical principles and applications of optical coherence tomography (OCT) have been described.\textsuperscript{15} The RNFL (3.4) scan (with 512 scan points) was selected for RNFL measurement. RNFL thickness was measured by averaging the results of 3 sequential circular scans with 3.4-mm diameters centered at the optic nerve head. The parameter, average RNFL thickness, is obtained in the analysis printout. A good-quality scan was defined as one with a signal-to-noise ratio of >35, 100% accepted A-scans, and well-delineated anatomic boundaries. A subject would be excluded from the study if the OCT image was not of good quality after 3 attempts. All OCT scans were of good quality, and no subject was excluded.

**Scanning Laser Polarimetry Measurements**

Scanning laser polarimetry (SLP) measurements were performed with the use of GDX VCC (Laser Diagnostic Technologies). Images were analyzed with software version 5.5.0. The principles and applications of SLP have been described elsewhere.\textsuperscript{16} The parameter TSINT average, equivalent to the average RNFL thickness, in the analysis printout was used in the study. Nine eyes were excluded in this study because of suboptimal scanning quality secondary to poor fixation, motion artifacts, or overilluminated images.

All measurements (VF sensitivity and OCT/SLP–measured RNFL thickness) were obtained within the same study period (August-November 2004).

**Statistical Analysis**

Differences in age, refraction, and VF MD among the diagnostic groups were evaluated with one-way ANOVA. Bonferroni correction was used for multiple comparisons. In all analyses, P < 0.05 was considered statistically significant.

Relationships between average RNFL thickness and visual sensitivity were evaluated with linear and nonlinear regression analyses. The linear model (y = ax + b) was compared with four common nonlinear models, including the second-order polynomial (y = ax^2 + bx + c), the third-order polynomial (y = ax^3 + bx^2 + cx + d), the first-order inverse (y = a ln(x) + b), and the logarithmic regressions (y = a log(x) + b). In regression analysis, the goodness-of-fit of any particular regression model is expressed as the coefficient of determination, R^2, which indicates how much of the total variation in the dependent variable can be accounted for by the regression function. However, it is not possible to determine whether model A is more correct than model B in describing the relationship profile based on the value of R^2 because the model with more parameters often has a higher R^2 than the model with fewer parameters. The extra-sum-of-square F test and the Akaike information criterion (AIC) are two mathematical approaches that take model complexity (the number of data points and
the number of parameters) into account in calculating the F ratio and the AIC difference, respectively, to determine which regression model to accept.

The F ratio is calculated by comparing the relative difference in the sum-of-square with the relative difference in the degrees of freedom of two nested (related) models. When comparing model A (the simpler model) and model B (the more complicated model),

\[
F \text{ ratio} = \frac{(SS_A - SS_B)}{(DF_A - DF_B)}
\]

where \(SS_A\) and \(SS_B\) are the sum-of-squares and \(DF_A\) and \(DF_B\) are the degrees of freedom of models A and B, respectively. Probability is then computed based on the F ratio. The hypothesis is to test whether the alternative nonlinear model is better than the linear model. If \(P < 0.05\), one can conclude that the alternative nonlinear model fits better than the linear model. If \(P > 0.05\), the null hypothesis would stipulate accepting the linear model. The major drawback in using the F ratio is that it only applies to nested models when one model has more parameters (i.e., is more complex) than the other. In the current analysis, the F test was used when comparing the linear, second-order, and third-order polynomials.

The AIC adopts another mathematical approach that can be used to compare nested and nonnested models. The concepts and applications of AIC have been described in detail by Burnham and Anderson.17 Because the logic behind AIC is not hypothesis testing, there is no \(P\) value in the calculation. The model with the lowest AIC is more likely to be correct, and the difference in corrected AIC (AICc) between model A and model B is defined as:

\[
AICc = AIC + \frac{2k(k+1)}{n-k-1}
\]

where \(AIC\) is the Akaike Information Criterion, \(k\) is the number of parameters, and \(n\) is the number of observations. If \(AICc_1 - AICc_2 < 2\), then the model with the lower AICc is preferred. If \(AICc_1 - AICc_2 \geq 2\), then there is no clear winner, and further analysis is required.

### Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Suspect</th>
<th>Glaucoma</th>
<th>(P^*)</th>
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<tbody>
<tr>
<td>No. of subjects</td>
<td>27</td>
<td>21</td>
<td>41</td>
<td>-</td>
</tr>
<tr>
<td>Age (yrs) mean ± SD</td>
<td>47.9 ± 13.8</td>
<td>55.9 ± 16.6</td>
<td>59.1 ± 11.7</td>
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<td>Refraction (D) mean ± SD</td>
<td>-0.37 ± 2.17</td>
<td>-1.35 ± 3.34</td>
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<td>Visual field MD (dB) mean ± SD</td>
<td>-1.47 ± 1.03</td>
<td>-1.42 ± 1.47</td>
<td>-11.1 ± 7.74</td>
<td>&lt;0.001‡</td>
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<td>TSNIT Average (μm) (GDX VCC)</td>
<td>55.26 ± 4.52</td>
<td>52.94 ± 5.47</td>
<td>38.66 ± 7.64</td>
<td>&lt;0.001‡</td>
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<tr>
<td>Average RNFLT (μm) (StratusOCT)</td>
<td>101.38 ± 7.73</td>
<td>96.91 ± 12.16</td>
<td>65.34 ± 14.08</td>
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* Analysis of variance with Bonferroni correction.
† Significant difference was noted between glaucoma and normal groups (\(P = 0.004\)).
‡ Significant differences were noted between glaucoma and normal groups (\(P < 0.001\)) and glaucoma and suspect groups (\(P < 0.001\)).

### Figure 1

**Scatter plot of visual field sensitivity, expressed in mean deviation (MD [dB]), against the retinal nerve fiber layer measured with GDX VCC (A) and StratusOCT (B). Linear and nonlinear regression models are compared with the F test and AICc. The best-fit model is highlighted with the corresponding regression profile, and the equation is indicated in the scatter plot. All subjects were included in the analysis \((n = 89)\).**

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AICcB - AICcA = N × ln (SSB/SSA) + 2K_B - 2K_A + 2K_B(K_B + 1)/(N - K_B - 1) - 2K_A(K_A + 1)/(N - K_A - 1)

where \( N \) is the number of data points, \( SS \) is the sum-of-square of the vertical distances of the points from the regression equations, and \( K \) is the number of parameters in the model plus 1. As in the F test, the difference in AICc is calculated with reference to the sum-of-squares and the number of parameters of the models compared. The probability that a particular model is correct in a comparison is given as:

\[
\text{Probability} = e^{-0.5(AICcB - AICcA)/(1 + e^{-0.5(AICcB - AICcA)})}
\]

The evidence ratio is defined as the probability that model A is correct divided by the probability that model B is correct. By convention, it is arranged to give a value greater than 1. Therefore, the evidence ratio should be interpreted with reference to the values of the probability of correct fitting. An evidence ratio of 2 describes one model as twice as likely to be correct as another. The difference in AICc is linearly correlated with the evidence ratio. In the present study, the linear model was compared with each of the nonlinear regression models. The probability of correct fitting, the difference in AICc, the evidence ratio, and the \( P \) value of the F test (in nested models only) were computed. All these parameters, though expressed in different forms, are in agreement with each other to determine which one is the best-fit regression model.

**RESULTS**

**Subject Characteristics**

Table 1 presents the baseline characteristics of the studied subjects. The average VF MD (±SD) of the glaucoma group was -11.1 ± 7.74 dB, with a range of VF defect from -2.36 dB to -30.00 dB.

**Regression Analyses of the Structure/Function Relationships with StratusOCT and GDx VCC**

The relationship profiles between RNFL thickness, as measured with StratusOCT and GDx VCC, and VF sensitivity, as expressed in MD (dB) and the unlogged 1/L, were analyzed using five different regression models (linear, second-order polynomials, third-order polynomials, inverse first-order, and logarithmic equations). When VF sensitivity MD (dB) was plotted against RNFL thickness, the third- and second-order polynomial models fit significantly better than the linear model in the GDx VCC (F test; \( P = 0.004 \)) and the StratusOCT RNFL measurements, respectively (F test; \( P < 0.001 \)) and demonstrated the largest difference in AICc (7.37 and 26.42 for GDx VCC and StratusOCT RNFL measurements, respectively) with respect to the linear regression models (Fig. 1). However, when VF sensitivity was expressed in the unlogged 1/L scale, simple linear fit had the best association with GDx VCC and StratusOCT RNFL measurements (Fig. 2).

Regression profiles were then reanalyzed with data obtained only from the glaucoma-suspect and glaucoma groups.

**Figure 2.** Scatter plot of visual field sensitivity, expressed in the unlogged 1/L scale, against the retinal nerve fiber layer measured with GDx VCC (A) and StratusOCT (B). Linear and nonlinear regression models are compared with the F test and AICc. The best-fit model is highlighted with the corresponding regression profile, and the equation is indicated in the scatter plot. All subjects were included in the analysis (\( n = 89 \)).
Similar to the analyses with the full data set, the structure/function relationship was better explained with nonlinear models when visual sensitivity in MD (dB) was plotted against RNFL thickness (Fig. 3). Logarithmic regression (in GDx VCC) and second-order polynomials (in StratusOCT) were found to be better regression models than linear regression, with differences in AICc of 1.55 and 12.95, respectively. By plotting VF sensitivity in 1/L against RNFL thickness, it was found that a nonlinear fit with the second-order polynomial was significantly better than a linear fit ($F$ test; $P = 0.048$; difference in AICc, 1.85) when the RNFL thickness was measured by GDx VCC (Fig. 4A). This is in contrast to the analysis in which a linear fit was better than a nonlinear fit when healthy subjects were included (Fig. 2A). However, linear regression remained the best-fit model when RNFL thickness was measured using StratusOCT (Fig. 4B).

**Relationship between AGIS/CIGTS Visual Field Scores and RNFL Thickness**

Visual field results in the glaucoma group ($n = 41$) were analyzed and translated to the AGIS and the CIGTS VF scores according to the methods described in the respective studies. Characteristics of the VF scores are illustrated in Table 2. The mean CIGTS VF score was higher than the mean AGIS VF score (10.57 versus 8.05; $P < 0.001$; paired $t$ test). AGIS and the CIGTS VF scores were highly correlated with each other and with the VF MD. Although the linear regression model best described the relationship between AGIS/CIGTS VF scores and GDx VCC-measured RNFL thickness (Figs. 5A and 6A), nonlinear first-order inverse regression was better fit than linear regression when plotting the AGIS/CIGTS VF scores against StratusOCT-measured RNFL thickness (differences in AICc were 2.81 and 3.49 for the AGIS VF score and the CIGTS VF score, respectively; Figs. 5B, 6B). In all the respective regression analyses, StratusOCT-measured RNFL thickness attained higher $R^2$ in association with different visual sensitivity measures (MD, 1/L, VF scores) than did the GDx VCC RNFL measurement.

**DISCUSSION**

The merits of studying structure/function profile with regression analysis are that regression analysis provides an effective way to understand the structure/function relationship in the course of progression in a cross-sectional manner and that the trend toward functional changes can be assessed with reference to an objective structural measurement at different stages of glaucoma. To make this type of analysis more useful or meaningful, we need better understanding of the dependence of the structure/function relationships on the choice of the perimetric scale, the type of measurement technique, and the composition of the study groups. In this study, emphasis was put on comparing the difference in data fitting between linear and each nonlinear regression model. Therefore, several nonlinear models may provide similar explanatory power better than that of the linear model. For example, in Figure 1A, although no direct comparison was made between the second- and the third-order polynomials in the data fitting based on the
evidence ratio, it is evident that the third-order polynomial is 39.74 times more likely to be correct than the linear model, whereas the second-order polynomial is only 25.05 times more likely to be correct. Although it is true that both the second- and the third-order polynomials fit better than the linear model, highlighting only one model would enable identifying the model with the highest evidence ratio and the largest difference in AICc. The strength of AIC in comparing linear and nonlinear models is that it selects the best model based on the probability of correct fitting but not of hypothesis testing. For that reason, the concept of power calculation is not applicable in AIC for regression model comparison. The fact that significant differences were found in the F test given the current sample size provides evidence that the sample size was adequate for detecting some existing differences.

The relationship between RNFL thickness and VF MD was found to be better fit with all the nonlinear models examined (best fit with the third- and the second-order polynomials for GDx VCC and StratusOCT RNFL measurements, respectively) compared with the linear model (Fig. 1). However, because healthy subjects and subjects with glaucoma were included in the analysis, one could argue that the flatter portion of the curve may represent the wide variations in RNFL thickness among healthy persons and may give the false impression of a functional reserve in the early stage of the disease (using OCT as an example, average RNFL thicknesses have been reported from 80 to 150 μm in various studies). To eliminate this factor, therefore, we excluded healthy persons in the second analysis (Fig. 3). It was confirmed that the nonlinear models were better than the linear model (best fit with the logarithmic and the second-order polynomials for the GDx VCC and the StratusOCT RNFL measurements, respectively) in analyzing the relationship between RNFL thickness and VF MD. These regression models describe a curvilinear structure/function relationship, suggesting that the progression of visual field loss, when it is expressed in MD (dB), increases during the course of

**Table 2. AGIS and CIGTS Visual Field Score Characteristics in the Glaucoma Group (n = 41)**

<table>
<thead>
<tr>
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<th>AGIS</th>
<th>CIGTS</th>
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<tr>
<td>Visual field score range</td>
<td>1-20</td>
<td>0.77-19.81</td>
</tr>
<tr>
<td>Mean score (± SD)</td>
<td>8.05 ± 5.68</td>
<td>10.57 ± 5.76</td>
</tr>
<tr>
<td>Correlation with MD (dB)</td>
<td><em>r = 0.97 (P &lt; 0.001)</em></td>
<td><em>r = 0.90 (P &lt; 0.001)</em></td>
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<tr>
<td>Correlation between AGIS and CIGTS VF scores</td>
<td><em>r = 0.904 (P &lt; 0.001)</em></td>
<td><em>r = 0.904 (P &lt; 0.001)</em></td>
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</tbody>
</table>

* Pearson coefficient of correlation (r).
the disease. This observation is also consistent with postmortem histologic measurement in patients with glaucoma, indicating that at least 25% to 35% of retinal ganglion cells were lost before abnormalities were statistically detected through automated visual field testing.22

When the visual field scale was expressed in unlogged 1/L, the relationship was best fit with linear models in GDx VCC and StratusOCT RNFL measurements (Fig. 2). However, when healthy subjects were excluded, a quadratic fit was better than a linear fit when the RNFL thickness was measured by GDx VCC, whereas StratusOCT-measured RNFL thickness remained best fit with linear regression (Fig. 4). The linear relationship has been described between visual field sensitivity in the unlogged 1/L scale and other parameters, including pattern-evoked electroretinogram (PERG) amplitude,23 Heidelberg retina tomography (HRT)-measured neuroretinal rim area,23 and GDx VCC–measured RNFL thickness.5 It was proposed that the structure/function change is linear and that it was the decibel scaling in the VF sensitivity that gave the impression of a functional reserve in the curvilinear relationship. In these clinical studies, however, only subjects with glaucoma with mild to moderate defect were included (the mean visual field MD SD in the glaucoma group was −4.15 ± 3.05 dB in the study by Garway-Heath et al.23 and −6.9 ± 5.6 dB in that by Schlottmann et al.5). Examining a full spectrum of glaucomatous optic neuropathy, from glaucoma suspect to end-stage glaucoma, would be essential to reveal the complete profile of the structure/function relationship. (In the present study, the mean visual field MD SD in the glaucoma group was −11.1 ± 7.74 dB; the range was −2.36 to −30.00 dB). The better fitting with a quadratic model in GDx VCC RNFL measurement among the glaucoma and glaucoma-suspect groups (Fig. 4A) suggested this relationship may vary with the composition of the study group. On the other hand, though first-order inverse regression best described the relationship between StratusOCT-measured RNFL and AGIS/CIGTS VF scores, it was the linear model that best fit in the relationships when RNFL thickness was measured by GDx VCC (Figs. 5, 6). Taking all these results into consideration, we concluded that the pattern of the structure/function relationship in glaucoma not only varied with the scale/method of expression in visual sensitivity, it depended on the choice of the RNFL imaging devices and the composition of the study groups.

The discrepancy in the regression profiles between OCT and SLP measurements in describing the relationship between RNFL thickness and VF sensitivity may stem from the intrinsic differences in the imaging principles of OCT and SLP, thus leading to the different estimations of RNFL thickness. The measurement of RNFL thickness in OCT is based on the differential reflectivity signals of the RNFL obtained using a scanning interferometer. It is calculated by measuring the difference between the vitreoretinal interface and the posterior border of the nerve fiber layer (which is identified with a predefined signal threshold algorithm). In contrast to OCT, SLP estimated the RNFL thickness by measuring the retardation of polarized scanning beams generated as a result of the form birefringence of the nerve fiber layer. It has been validated that good correlation was found between retardation and the histopathologic measurement of RNFL thickness, and a constant proportion was adopted for calculation of RNFL thickness in micrometer in relation to the measured retardation in nanometer.24 Yet it was recently reported that the birefringence retardation de-

<table>
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<tr>
<th>Regression Model</th>
<th>R²</th>
<th>Probability of Correct Fitting</th>
<th>Evidence Ratio</th>
<th>Absolute Difference in AICc</th>
<th>F test (P value)</th>
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<td>Linear</td>
<td>0.348</td>
<td>-</td>
<td>77.31% / 22.69%</td>
<td>3.41</td>
<td>2.49</td>
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<tr>
<td>2nd order polynomial</td>
<td>0.348</td>
<td>-</td>
<td>92.51% / 7.49%</td>
<td>5.03</td>
<td>-</td>
</tr>
<tr>
<td>3rd order polynomial</td>
<td>0.348</td>
<td>-</td>
<td>52.31% / 47.69%</td>
<td>1.10</td>
<td>-</td>
</tr>
<tr>
<td>Logarithmic</td>
<td>0.345</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Inverse</td>
<td>0.332</td>
<td>-</td>
<td>62.66% / 37.31%</td>
<td>1.68</td>
<td>1.04</td>
</tr>
</tbody>
</table>

![FIGURE 5. Scatter plot of visual field sensitivity, expressed in the AGIS VF score, against the retinal nerve fiber layer measured with GDx VCC (A) and StratusOCT (B). Linear and nonlinear regression models are compared with the F test and AICc. The best-fit model is highlighted with the corresponding regression profile, and the equation is indicated in the scatter plot. Only data from patients with glaucoma were included (n = 41).](http://iovs.arvojournals.org/doi/10.1167/iovs.04-383)
tected by SLP actually varied with the position around the optic nerve head. As a result, using a constant proportion for calculation of RNFL thickness may not reflect the true thickness in some sectors around the optic nerve head. Furthermore, changes in the SLP measurements could result from the changes in either RNFL thickness or RNFL birefringence. Morphologic alteration like gliosis, partial loss of organelles, or shrinkage of ganglion cells might lead to changes in the birefringence pattern before the irreversible loss of axons. Therefore, variations in the regression profiles of the structure/function relationship may signify the difference in the inherent measuring capacity between OCT and SLP. In the present study, the OCT RNFL measurements attained higher associations with visual function in all the respective regression analyses compared with the GDx VCC RNFL measurements. In addition, plotting of the OCT RNFL measurements against MD (dB) and the unlogged 1/L scale demonstrated consistent curvilinear and linear relationships, respectively (Figs. 1B, 2B, 3B, 4B), which is in greater agreement with the results from the histologic study in experimental glaucoma investigating the association between ganglion cell loss and decrease in VF sensitivity. It was reported that the relationship between sensitivity loss (in decibels) and ganglion cell loss (in percentages) was curvilinear and that it changed to a linear function when both VF sensitivity and ganglion cell loss were expressed in decibels. Collectively, we believe the use of StratusOCT may provide a better approach to understanding the structure/function relationship in glaucoma than the use of GDx VCC.

One of the most controversial risk factors for predicting progression is the severity of the baseline VF. Despite a number of prospective studies performed to investigate whether the initial VF had any predictive power for subsequent progression, different conclusions were reached. In the CIGTS, it was found that patients with higher VF scores at baseline had higher VF scores during follow-up. This was repeated by the results in the Early Manifest Glaucoma Trial (EMGT), which reported an increased risk for progression in patients with MD worse than -4 dB. Conversely, the AGIS found that lesser VF defect increased the risk for additional VF loss. Interestingly, using the same AGIS VF scoring system, Chen and Park showed that an increased initial AGIS score was associated with progression. Although most studies supported the finding that increased severity of initial visual field was associated with further visual field worsening, others showed no association, and a few arrived at the same conclusions reported in the AGIS. In the present study, regression analysis revealed that first-order inverse regression best described the relationship between the AGIS/CIGTS VF scores and StratusOCT-measured RNFL thickness (Figs. 5B, 6B). Assuming the rate of loss of the retinal ganglion cell and its nerve fiber in glaucoma is constant during progression, our results provide an explanation for the findings in those longitudinal studies showing that increased severity of VF defect (documented by the AGIS/CIGTS VF scores or MD) at baseline indicates higher risk for progression. For the same degree of structural damage (reduction in RNFL thickness), the decrease in VF score or decibel is more dramatic in the advanced stages of the disease than in the early stages. For example, based on the regression functions in the study (Figs. 5B, 6B), a reduction in RNFL thickness from 80 to 70 μm (in the early stage) would lead to a corresponding increase in the AGIS score of 2.0 and in the CIGTS score of 2.1. When the RNFL thickness is reduced from 50 to 40 μm (in the advanced stage), the corresponding increase in the AGIS and the CIGTS scores would be 5.7 and 5.9.
respectively. Therefore, it is easier to detect the change in VF progression in VF scores during the moderate/advanced stages of disease, leaving the impression of increased risk for progression when the baseline VF scores are high. Therefore, the current AGIS and CIGTS scoring systems are considered less sensitive for detecting progression in the early stages of glaucoma because the steps for progression (an increase in score of 4 in the AGIS and 3 in the CIGTS) is defined independently of the disease stage. Consistent with earlier investigations, we demonstrated the CIGTS VF scores were systematically higher than the AGIS VF scores, and both scorings were highly correlated with each other and with the VF MD. Our results are also consistent with the findings of longitudinal studies showing that the CIGTS scoring method leads to higher rates of detection of disease progression than the AGIS scoring system.

StratusOCT and GDx VCC are the latest versions of commercially available nerve fiber analyzers, but longitudinal data are still lacking regarding the change in RNFL during glaucoma progression. It is unknown whether the rate of loss of RNFL is constant at different stages of glaucoma; in addition, the temporal relationship in structure/function change is not completely understood. Knowing these factors would have great impact on the interpretation on the structure/function regression profile. A prospective follow-up study is essential to cross-validate the structure/function regression models.

Conclusions

In summary, we found the relationship between RNFL thickness and VF sensitivity varied not only with the scales and methods of VF expression (MD, unlogged 1/L, and VF scores) but with the type of RNFL imaging devices (OCT versus SLP) and the characteristics of the studied groups. Although determining true progression remains a major challenge in the management of glaucoma, quantitative nerve fiber layer imaging may offer a new paradigm for understanding glaucoma progression and may serve as an objective standard to correlate with functional loss.

References