Diffuse Glaucomatous Structural and Functional Damage in the Hemifield Without Significant Pattern Loss

Dilraj S. Grewal, MD; Mitra Sehi, PhD; David S. Greenfield, MD

Objectives: To compare the retinal nerve fiber layer (RNFL) thickness and retinal sensitivity in the normal visual hemifield of glaucomatous eyes with localized visual field loss with those of normal eyes and eyes with suspected glaucoma, and to evaluate the relationship between RNFL atrophy and glaucoma severity.

Methods: One randomly selected eye of each subject underwent standard automated perimetry, stereoscopic photography, scanning laser polarimetry with enhanced corneal compensation, and time-domain and spectral-domain optical coherence tomography (OCT). Mean retinal sensitivity values were calculated in the normal standard automated perimetry hemifield of the glaucoma group and randomly selected hemifields in the normal and suspected glaucoma groups. The mean RNFL thickness values corresponding to the normal hemifield were calculated. Glaucoma severity was judged using standard automated perimetry pattern standard deviation and the Heidelberg retina tomograph–derived linear cup-disc ratio.

Results: Fifty subjects were enrolled in each group. Mean RNFL thickness in the normal hemifield obtained using spectral-domain OCT, time-domain OCT, and scanning laser polarimetry with enhanced corneal compensation was significantly (P ≤ .01) thinner in the glaucoma group compared with the normal and suspected glaucoma groups. Mean retinal sensitivity in the normal hemifield was significantly (P < .001) reduced in the glaucoma group compared with the normal and suspected glaucoma groups. The Heidelberg retina tomograph–derived cup-disc ratio was significantly correlated with mean RNFL thickness in the normal hemifield obtained using spectral-domain OCT, time-domain OCT, and scanning laser polarimetry with enhanced corneal compensation (P ≤ .01).

Conclusions: Diffuse RNFL atrophy and retinal sensitivity loss exist in glaucomatous eyes with localized standard automated perimetry deficits. Glaucomatous damage affects both structure and function in a linear proportion.


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EXAMINATION AND DOCUMENTATION of the optic disc and retinal nerve fiber layer (RNFL) are essential for the diagnosis and monitoring of glaucoma. Imaging technologies such as confocal scanning laser ophthalmoscopy (CSLO) (Heidelberg Retina Tomograph; Heidelberg Engineering GmbH, Heidelberg, Germany), scanning laser polarimetry (SLP) (Carl Zeiss Meditec Inc, Dublin, California), and optical coherence tomography (OCT) (Carl Zeiss Meditec Inc) provide objective and quantitative measurements that are highly reproducible and show good agreement with clinical estimates of optic nerve head structure and visual function. Recent technological advances have emerged that may enable more precise identification and quantification of glaucomatous damage and facilitate early glaucoma diagnosis and monitoring of progression. Enhanced corneal compensation (ECC) has been reported to improve the signal to noise ratio and eliminate atypical birefringence artifact associated with SLP, to increase the concordance between structure and function, and to improve the discriminating power for glaucoma diagnosis. Compared with time-domain OCT (TD-OCT), spectral-domain OCT (SD-OCT) provides significantly increased scanning speed and resolution and permits high-density raster scanning of retinal tissue and reduction of ocular motion artifact.

There are reports of diffuse RNFL damage in eyes with localized visual field abnormalities. Bagga et al investigated the incidence of RNFL atrophy in 90° to 120° quadrants corresponding to normal visual hemifields in a small population of individuals with glaucomatous eyes and with visual field loss localized to the opposite hemifield. When the researchers compared 20 eyes with glaucomatous hemifield abnormalities and age-matched control eyes, they identified significant RNFL atrophy in the apparently non-glaucomatous sectors in 75% of the eyes measured using SLPECC and 90% of the eyes measured using TD-OCT. Comparisons of incongruous regions of visual sensitivity and RNFL thickness, small sample size, and inclusion of eyes with imaging artifact—including incom-
complete corneal compensation when using SLPECC\textsuperscript{18-21} or the low signal strength when using OCT\textsuperscript{22,23} that is sometimes identified—have been obstacles toward the validation of this theory.

We hypothesized that recent advancements in structural imaging technology may better quantify the presence of diffuse glaucomatous RNFL atrophy in eyes with localized visual field abnormalities. The objectives of the present investigation were to quantify the RNFL thickness in the normal hemifield in a population of individuals with normal eyes, patients with suspected glaucoma, and patients with glaucoma and to evaluate the relationship between RNFL atrophy in the apparently normal hemifield and glaucoma severity using TD-OCT, SD-OCT, and SLPECC.

Methods

Informed consent was obtained from all subjects by using a consent form approved by the Institutional Review Board for Human Research of the University of Miami Miller School of Medicine, which was in agreement with the provisions of the Declaration of Helsinki. Participants consisted of the following 3 groups: volunteers with normal eyes, patients with suspected glaucoma, and patients with perimetric glaucoma. All participants underwent a complete ophthalmic examination, including slitlamp biomicroscopy, gonioscopy, ultrasonographic pachymetry, Goldmann applanation tonometry, dilated stereoscopic examination, stereoscopic photography of the optic disc, and 2 reliable standard automated perimetry (SAP) examinations. The SAP was performed with the Humphrey field analyzer (SITA standard strategy, program 24-2; Carl Zeiss Meditec Inc).

Inclusion criteria common to all 3 groups consisted of refractive error ranging from \(-8.00\) to \(+4.00\) diopters, best-corrected visual acuity equal to or better than 20/40, age range from 40 to 85 years, reliable SAP results (<33\% rate of fixation losses and positive and false-negative findings), and no history of intraocular surgery except for uncomplicated cataract extraction. Subjects with ocular disease other than glaucoma or cataract, best-corrected visual acuity worse than 20/40, peripapillary atrophy extending to 1.7 mm from the center of the optic disc, or unreliable SAP results were excluded. One eye per subject was randomly selected for enrollment.

Individuals in the normal eyes group had an intraocular pressure of at least 24 mm Hg, normal optic discs, and normal SAP results, or those with glaucomatous optic neuropathy characterized by an intraocular pressure of at least \(15 \text{ mm Hg}\), normal optic discs, and normal SAP results, or glaucoma hemifield test result and a PSD outside 95\% normal limits, or patients with SAP abnormalities who had at least 1 confirmatory result on a visual field examination. The glaucomatous hemifield had a cluster of 3 or more contiguous points in the pattern deviation plot with a probability of less than 5\%, with at least 1 of them having a probability level of less than 1\%. The opposite, apparent normal hemifield had no point worse than the 2\% probability level on the pattern deviation plot.

Retinal Sensitivity

Mean retinal sensitivity values in the apparently normal SAP hemifield were calculated using the average of 26 of the 52 test locations within the normal hemifield (Figure 1). In the normal eyes and suspected glaucoma groups, the normal hemifield was selected randomly and mean retinal sensitivity was calculated in a similar fashion.

Optic Disc and RNFL Imaging

All subjects underwent imaging using SD-OCT (RTVue, software version A3.0.1.16; Optovue Inc, Fremont, California), TD-OCT (Stratus OCT, software version 4.0.7; Carl Zeiss Meditec Inc), and SLPECC (GDxECC, software version 6.0; Carl Zeiss Meditec Inc). An average of 2 consecutive scans was obtained on the same day by the same examiner (D.S.G.) through undilated pupils; the average of 2 high-quality measurements was used for the analysis. With all 3 technologies, RNFL thickness was calculated in a similar fashion.
measurements were generated using a uniform 3.4-mm-diameter peripapillary measurement circle. The RNFL thickness values were calculated from a 180° peripapillary segment corresponding to the apparently normal SAP hemifield. Enrollment criteria for the selection of high-quality images included absence of eye movement during scan acquisition, well-focused and well-centered images, and a Q score of at least 8 (SLPECC), a signal strength of at least 6 (TD-OCT), and a scan score index of at least 30 (SD-OCT).

Peripapillary retardation measurements using SLPECC were generated using a fixed 0.4-mm-wide concentric band centered on the optic disc, with a 3.2-mm outer diameter and a 2.4-mm inner diameter. A primary scan was obtained before each measurement to compensate for the corneal birefringence. Thirty-two of 64 peripapillary segments, each corresponding to a 3.625° measurement arc, were extracted using a data export file, and a mean hemifield RNFL thickness value corresponding to the apparently normal SAP hemifield was calculated.

The TD-OCT imaging of the peripapillary RNFL was performed using a fast RNFL acquisition protocol, which generates an average of 3 peripapillary scans (256 A-scans per 360° circular path, with each A-scan corresponding to a 1.406° arc) with a diameter of 3.4 mm centered on the optic disc and a scan acquisition time of approximately 1 second. Data from 128 A-scans corresponding to the normal SAP hemifield were exported and averaged to calculate a mean hemifield RNFL thickness value. The SD-OCT imaging of the peripapillary RNFL was performed using a fast RNFL acquisition protocol, which generates an average of 4 peripapillary scans (999 A-scans per 360° circular path, with each A-scan corresponding to a 0.36° arc) with a diameter of 3.45 mm centered on the optic disc and a scan acquisition time of 76 milliseconds. Data from 499 A-scans corresponding to the normal hemifield were exported and averaged to calculate a mean hemifield RNFL thickness value. For TD-OCT and SD-OCT, images with failure of the RNFL segmentation algorithm were excluded.

A subset of 127 of the 150 patients (84.7%) underwent imaging with CSLO (Heidelberg Retina Tomograph II, software version 1.4.1.0; Heidelberg Engineering GmbH) for assessment of the linear cup-disc ratio (CDR). Linear CDR measurements obtained with CSLO have been shown to correlate highly with independent expert assessment of vertical CDR determined using stereoscopic disc photographs.25,26

### Statistical Analysis

Statistical analysis was performed using commercially available software (SPSS, version 15.0 [SPSS Inc, Chicago, Illinois] and STATISTICA, version 8.0 [StatSoft Inc, Tulsa, Oklahoma]). Analysis of variance with the Tukey honestly significant difference test of multiple comparisons for all variables except gender and ethnicity, which were analyzed using the χ² test.

<table>
<thead>
<tr>
<th>Valuea</th>
<th>Table 1. Clinical Characteristics of the 150 Subjects in the Study Populationb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Eyes Group (n=50)</td>
<td>Suspected Glaucoma Group (n=50)</td>
</tr>
<tr>
<td><strong>Age, y</strong> 66.8 (9.0) [44 to 80]</td>
<td>66.7 (9.4) [41 to 86]</td>
</tr>
<tr>
<td><strong>Gender, No. of subjects</strong></td>
<td></td>
</tr>
<tr>
<td>Male 28</td>
<td>20</td>
</tr>
<tr>
<td>Female 22</td>
<td>30</td>
</tr>
<tr>
<td><strong>Ethnicity, No. of subjects</strong></td>
<td></td>
</tr>
<tr>
<td>Asian 0</td>
<td>2</td>
</tr>
<tr>
<td>Black 2</td>
<td>3</td>
</tr>
<tr>
<td>Non-Hispanic white 44</td>
<td>42</td>
</tr>
<tr>
<td>Hispanic 4</td>
<td>3</td>
</tr>
<tr>
<td><strong>SAP MD, dB</strong> -0.4 (1.6) [-4.4 to 1.9]</td>
<td>-0.4 (1.3) [-3.7 to 1.9]</td>
</tr>
<tr>
<td><strong>SAP PSD, dB</strong> 1.6 (0.5) [1.0 to 3.9]</td>
<td>1.6 (0.5) [1.1 to 4.0]</td>
</tr>
<tr>
<td><strong>Mean CSLO linear CDRc</strong> 0.4 (0.2) [0.1 to 0.8]</td>
<td>0.5 (0.2) [0.1 to 0.8]</td>
</tr>
<tr>
<td><strong>SD-OCT average RNFL thickness, µm</strong> 93.4 (13.2) [70.0 to 127.0]</td>
<td>99.2 (11.4) [74.5 to 125.5]</td>
</tr>
<tr>
<td><strong>TD-OCT average RNFL thickness, µm</strong> 83.6 (10.6) [69.8 to 116.0]</td>
<td>82.4 (10.6) [71.4 to 118.4]</td>
</tr>
<tr>
<td><strong>SLPECC TSNIT average, µm</strong> 93.4 (13.2) [70.0 to 127.0]</td>
<td>99.2 (11.4) [74.5 to 125.5]</td>
</tr>
<tr>
<td><strong>Mean CSLO linear CDRc</strong> 0.4 (0.2) [0.1 to 0.8]</td>
<td>0.5 (0.2) [0.1 to 0.8]</td>
</tr>
</tbody>
</table>

Abbreviations: CDR, cup-disc ratio; CSLO, confocal scanning laser ophthalmoscopy; MD, mean deviation; PSD, pattern standard deviation; RNFL, retinal nerve fiber layer; SAP, standard automated perimetry; SD-OCT, spectral-domain optical coherence tomography; SLPECC, scanning laser polarization with enhanced corneal compensation; TD-OCT, time-domain OCT; TSNIT, temporal-superior-nasal-inferior-temporal.

a Unless otherwise indicated, data are expressed as mean (SD) [range].

b The difference between groups was determined using analysis of variance with the Tukey honestly significant difference test of multiple comparisons for all variables except gender and ethnicity, which were analyzed using the χ² test.

c For normal vs suspected glaucoma, P = .93; normal vs glaucoma, P = .06; and suspected glaucoma vs glaucoma, P = .051.

d Indicates the glaucoma group compared with the normal eyes and suspected glaucoma groups.

e N = 127.

We enrolled 150 eyes of 150 subjects. Participants included 50 volunteers with normal eyes (mean age, 66.8 [9.1] years), 50 patients with suspected glaucoma (mean age, 66.7 [9.4] years), and 50 patients with glaucoma (mean age, 70.4 [10.3] years) (normal vs suspected glaucoma, P = .93; normal vs glaucoma, P = .06; and suspected glaucoma vs glaucoma, P = .051) (P > .05). Table 1 provides the clinical characteristics of the study population. There were no differences among the 3 groups with regard to age, gender, or ethnicity. In the glaucoma group, the glaucomatous visual field defect was localized to the superior hemifield in 27 of 50 eyes (54%) and to the inferior visual hemifield in 23 of 50 eyes (46%). Glaucoma...
matous eyes had significantly lower SAP mean deviation (P < .001); significantly lower mean RNFL thickness as measured using SD-OCT, TD-OCT, and SLPECC (P < .001); and significantly greater SAP PSD and CSLO-derived linear CDR values (P < .001) compared with the normal and suspected glaucoma groups. There was no significant difference between the normal and suspected glaucoma groups in average SAP mean deviation (P > .99) or average RNFL thickness measured using SD-OCT (P = .44), TD-OCT (P = .30), or SLPECC (P = .30). Mean RNFL thickness measured using SD-OCT was significantly greater compared with mean RNFL thickness measured using TD-OCT in the normal eye group (P = .001), the suspected glaucoma group (P = .001), and the glaucoma group (P = .02).

Table 2 compares the mean retinal sensitivity and RNFL thickness values corresponding to the normal SAP hemifield among the 3 groups (n = 150). Mean hemifield retinal sensitivity was significantly (P < .001) less in the glaucoma group than in the normal eyes group and the suspected glaucoma group. Mean hemifield RNFL thickness in the glaucoma group measured using TD-OCT and SD-OCT were significantly less (P = .05 to P = .001) compared with the suspected glaucoma group and the normal eyes group. No differences were observed between the suspected glaucoma and normal eyes groups in hemifield retinal sensitivity (P = .60) or in hemifield RNFL thickness measured using TD-OCT (P = .30), SD-OCT (P = .40), or SLPECC (P = .10).

Table 3 summarizes the correlation between retinal sensitivity and RNFL thickness in the normal SAP hemifield and glaucoma severity defined by structure (CSLO-derived linear CDR) and function (visual field PSD) in the suspected glaucoma and glaucoma groups. Hemifield RNFL thickness measured using SD-OCT, TD-OCT, and SLPECC was significantly associated (P = .002 to P < .001) with CDR. Hemifield RNFL thickness measured using TD-OCT and SLP was significantly associated with SAP PSD (P = .01 and P = .02, respectively). The relationship between RNFL atrophy in the normal hemifield and glaucoma severity judged by CSLO-derived linear CDR and SAP PSD is illustrated in Figure 2 for the entire cohort. The CDR was significantly correlated with mean hemifield RNFL thickness measured using SD-OCT (P = .002), TD-OCT (P = .001), and SLPECC (P = .01) in this cohort. The CDR was not significantly correlated (r = −0.12; P = .18) with the retinal sensitivity when it was converted using a scale of 1/lambert. The SD-OCT demonstrated similar correlation with glaucomatous structural (P = .27) and functional damage (P = .37) in the apparently normal SAP hemifield compared with TD-OCT using a test of homogeneity with correlated data. The SAP PSD was significantly correlated with mean hemifield RNFL thickness using SD-OCT (r = .17; P = .03), TD-OCT (r = −.27; P < .001), and SLPECC (r = −0.27; P < .001) across the entire cohort.

We evaluated the correlation between RNFL thickness (in micrometers) and the visual sensitivity values using a linear scale of 1/lambert in the glaucomatous hemifield (n = 50) and the apparently normal hemifield (n = 150). The visual sensitivity was significantly correlated with RNFL thickness in the glaucomatous hemifield measured using SD-OCT (r = .45; P = .001), TD-OCT (r = .28; P = .05), and SLPECC (r = .34; P = .02); and in the apparently normal hemifield measured using SD-OCT (r = .34; P < .001), TD-OCT (r = .26; P = .001), and SLPECC (r = .22; P = .008).

### Table 2. Mean Retinal Sensitivity and RNFL Thickness Values Corresponding to Normal Standard Automated Perimetry Hemifields in 150 Eyes

<table>
<thead>
<tr>
<th>Normal Hemifield Variables</th>
<th>Normal Eyes Group (n=50)</th>
<th>Suspected Glaucoma Group (n=50)</th>
<th>Glaucoma Group (n=50)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal sensitivity, dB</td>
<td>28.9 (1.7) [25.0-31.5]</td>
<td>29.3 (1.6) [25.1-32.9]</td>
<td>27.8 (1.7) [23.5-30.9]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SD-OCT RNFL thickness, µm</td>
<td>103.3 (17.1) [59.0-131.0]</td>
<td>98.6 (13.4) [66.0-124.5]</td>
<td>90.6 (19.3) [57.0-130.0]</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>TD-OCT RNFL thickness, µm</td>
<td>95.4 (12.7) [66.0-129.3]</td>
<td>91.1 (12.1) [67.6-118.4]</td>
<td>82.3 (17.1) [53.8-126.1]</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>SLPECC RNFL thickness, µm</td>
<td>50.0 (5.8) [39.4-70.3]</td>
<td>47.1 (6.0) [36.5-63.0]</td>
<td>43.0 (8.7) [23.2-61.4]</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

### Table 3. Correlation Between Retinal Sensitivity and RNFL Thickness in the Normal SAP Hemifield, CSLO Linear CDR, and Visual Field PSD in Suspected Glaucoma and Glaucoma Groups

<table>
<thead>
<tr>
<th>Normal Hemifield Variables</th>
<th>CSLO Linear CDR (n=95)</th>
<th>SAP PSD (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correlationa</td>
<td>P Value</td>
</tr>
<tr>
<td>Retinal sensitivity, dB</td>
<td>−0.12</td>
<td>.13</td>
</tr>
<tr>
<td>SD-OCT RNFL thickness, µm</td>
<td>−0.31</td>
<td>.001</td>
</tr>
<tr>
<td>TD-OCT RNFL thickness, µm</td>
<td>−0.42</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SLPECC RNFL thickness, µm</td>
<td>−0.29</td>
<td>.002</td>
</tr>
</tbody>
</table>

Abbreviations: See Table 1.

a Calculated using analysis of variance with Tukey honestly significant difference test of multiple comparisons. Comparisons are for the glaucoma group compared with the normal eyes and suspected glaucoma groups.

b Calculated using linear regression analysis.
Tension Glaucoma Study,36 respectively. Other factors may contribute to this observation, including the method by which end points are assessed and the stage of glaucoma severity.37 Imaging technologies have the potential to identify relevant structural efficacy end points in randomized clinical trials and have taken on an expanded role in glaucoma clinical care.38 Confocal scanning laser ophthalmoscopy–derived linear cup-disc ratio and mean retinal nerve fiber layer (RNFL) thickness in the normal hemifield obtained using time-domain optical coherence tomography (TD-OCT, left), spectral-domain OCT (SD-OCT, middle), and scanning laser polarimetry with enhanced corneal compensation (SLPECC) (right) in the study population (n=127). The cup-disc ratio was significantly correlated with mean hemifield RNFL thickness obtained using TD-OCT (r=-0.35; P<.001), SD-OCT (r=-0.29; P=.002), and SLPECC (r=-0.24; P=.01). B. The relationships are shown between standard automated perimetry pattern standard deviation (SAP PSD) and mean (RNFL) thickness in the normal hemifield obtained using TD-OCT, SD-OCT, and SLPECC in the study population (n=150). We found a significant correlation between SAP PSD and mean hemifield RNFL thickness obtained using TD-OCT (r=-0.27; P<.001), SD-OCT (r=-0.18; P=.03), and SLPECC (r=-0.27; P<.001).

Many studies have examined the relationship between structure and function in glaucomatous optic neuropathy. Structure and function are often well correlated in glaucoma,28,29 however, anatomical and physiological changes may occur at different times throughout the natural history of the disease. Glaucomatous structural changes may occur within astroglia and other tissues that support the retinal ganglion cells and their axons, and SAP abnormalities may result from dysfunctional cells that have not yet undergone death or atrophy.30-32 Glaucoma clinical trials often do not support concurrent changes in structure and function. In the Ocular Hypertension Treatment Study,33 only 12 of 125 end points were characterized by a change in both the optic disc and visual field, and none of the 106 end points in the European Glaucoma Prevention Study34 demonstrated a change in both structure and function. Among eyes with established glaucomatous optic nerve damage and progressive disease, 0.8% and 11% demonstrated detectable structural end points in the Early Manifest Glaucoma Trial35 and the Collaborative Normal-Tension Glaucoma Study,36 respectively. Other factors may contribute to this observation, including the method by which end points are assessed and the stage of glaucoma severity.37 Imaging technologies have the potential to identify relevant structural efficacy end points in randomized clinical trials and have taken on an expanded role in glaucoma clinical care.38 Confocal scanning laser ophthalmoscopy has been studied in the European Glaucoma Prevention Study34 and in an ancillary study of the Ocular Hypertension Treatment Study.38 Topographic measurements generated with CSLO have been demonstrated to correlate highly with clinical estimates of the optic nerve generated using expert assessment at an independent reading center after correction for optic disc size.39 Recent advances in imaging technology enable more robust quantification of RNFL thickness with significant reduction in imaging artifact. The SLP technology uses a new strategy for corneal compensation and has been reported to significantly reduce atypical birefringence and enhance glaucoma diagnosis.40-42 Compared with TD-OCT, which collects 400 axial measurements per second with an axial resolution of approximately 10 µm, SD-OCT allows scan rates of 20 000 axial measurements per second with an axial resolution of 5 µm.43

The present study demonstrates that eyes with localized SAP defects have evidence of diffuse attenuation in RNFL thickness and retinal sensitivity in apparently normal areas of the visual field. Our definition of normal was based on the criteria in our study, which is consistent with the literature.13,14,16,43 Our method differs from those used...
by others.\textsuperscript{12,14,15,43} We used OCT technology with high speed and high resolution\textsuperscript{44} and SLPECC with augmentation of the signal to noise ratio and compared retinal hemispheres with corresponding 180° assessments of structure and function. Unique to our investigation, we found that RNFL atrophy in the apparently normal SAP hemifield was linearly proportional to glaucoma severity judged independently by CSLO-derived measurements of CDR and visual field PSD. Also, although achromatic perimetric abnormalities, as defined in this protocol, were absent from the apparently normal visual hemifield, significant loss in retinal sensitivity was similarly observed with increased glaucoma severity. The linear relationship, observed between RNFL thickness (in micrometers) and sensitivity values (1/lambert) in glaucomatous and apparently normal visual hemifields, further suggests that the structure-function relationship is proportional to the severity of glaucomatous damage. Selective perimetric techniques such as short wavelength and frequency-doubling perimetry have been demonstrated to have increased sensitivity for the detection of early glaucomatous changes.\textsuperscript{43,45-49}

Glaucomatous optic neuropathy has been described as a continuum\textsuperscript{50} in which retinal ganglion cell dysfunction eventually leads to cell death and atrophy through multifactorial mechanisms. Despite the use of high-resolution structural imaging, the suspected glaucoma group could not be differentiated from the normal eyes group. This finding is consistent with the literature,\textsuperscript{50-53} which demonstrates conflicting evidence regarding the ability to differentiate these groups using selective testing. Several factors may explain this observation. Our cohort of eyes with suspected glaucoma consisted of eyes with ocular hypertension and/or glaucomatous optic nerve damage but with normal SAP results. It is possible that we might not have identified a population enriched with sufficient risk for glaucomatous injury. Furthermore, to avoid selection bias, structural assessments in the normal and suspected glaucoma groups involved randomly selected retinal hemifields that may have been insufficiently robust to demonstrate differences between these groups. As demonstrated in Table 1, comparisons of mean peripapillary RNFL thickness measured using SD-OCT, TD-OCT, and SLPECC were similar in the normal eyes and suspected glaucoma groups.

Retinal nerve fiber layer thickness is inversely proportional to the distance from the optic nerve head at which it is measured.\textsuperscript{54,55} To control for this confounding factor, all RNFL measurements were obtained with a peripapillary measurement circle using a fixed diameter of approximately 3.4 mm. We hypothesized that SD-OCT would be more robust for quantifying narrow regions of RNFL atrophy based on measurements generated with 499 A-scans per retinal hemifield compared with 128 A-scans measured with TD-OCT and 32 peripapillary sectors measured with SLPECC. Despite having a higher resolution and a faster scanning speed than TD-OCT, SD-OCT demonstrated similar correlation with glaucomatous structural and functional damage in the apparently normal SAP hemifield. We speculate that 2-dimensional imaging that uses cross-sectional slices is less robust than regional maps of the peripapillary RNFL. Further development and refinement of SD-OCT segmentation techniques may provide 3-dimensional measurement of RNFL volume and perhaps direct quantification of the retinal ganglion cell layer. These assessment techniques are likely to be more sensitive for detection of early glaucomatous damage and are currently in development. Finally, a mismatch between the sizes of the examined areas (the SITA standard strategy, program 24-2, vs a 3.4-mm measurement circle with SD-OCT and TD-OCT) may also influence the structure-function correlation. Converting the retinal sensitivity values to the 1/lambert scale did not improve the correlation between CDR and retinal sensitivity values in linear mode.

In conclusion, diffuse RNFL atrophy and retinal sensitivity loss exist in glaucomatous eyes with localized SAP deficits and are linearly proportional to glaucoma severity. The RNFL imaging techniques of SD-OCT, TD-OCT, and SLPECC demonstrate similar performance for quantifying structural changes in the apparently normal SAP hemifield of eyes with localized visual field loss.

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Author Contributions: All of the authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES


