Macular Thickness Changes in Glaucomatous Optic Neuropathy Detected Using Optical Coherence Tomography

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Objective: To correlate macular thickness and retinal nerve fiber layer (RNFL) thickness in normal and glaucomatous eyes using optical coherence tomography.

Methods: Complete examination, automated achromatic perimetry, and optical coherence tomography of the peripapillary RNFL and macula were performed. Exclusion criteria were visual acuity of less than 20/40, diseases other than glaucoma, and unreliable automated achromatic perimetry. Macular thickness measurements were generated using 6 radial optical coherence tomographic scans (5.9 mm) centered on the fovea, and mean and quadrant macular thickness values were calculated.

Results: Fifty-nine eyes of 59 patients (29 normal and 30 glaucomatous) were enrolled (mean±SD age, 56.7±20.3 years; range, 20-91 years). All eyes with glaucoma had associated visual field loss (mean±SD mean defect, −8.4±5.8 dB). Mean macular thickness was significantly associated with visual field mean defect (R²=0.47; P<.001), pattern standard deviation (R²=0.32; P<.001), and mean RNFL thickness (R²=0.38; P<.001). In glaucomatous eyes with visual field loss localized to 1 hemifield (n=11), mean±SD macular thickness in the quadrant associated with the field defect (277±28 µm) was significantly less (P=.005) than in the unaffected quadrant (286±27 µm). Mean RNFL thickness in the affected quadrant (89±53 µm) was significantly thinner (P=.009) than in the unaffected quadrant (121±39 µm).

Main Outcome Measures: Mean total and quadrant macular and RNFL thickness measurements.

Conclusions: Macular thickness changes are well correlated with changes in visual function and RNFL structure in glaucoma and may be a surrogate indicator of retinal ganglion cell loss.

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In glaucoma, the essential pathologic process is the loss of retinal ganglion cells and their axons.1 Numerous studies have shown that glaucomatous damage to the retinal nerve fiber layer (RNFL) precedes functional loss by as much as 5 years.2-7 Loss of the retinal ganglion cells and their axons is also known to occur in the posterior pole, where these cells may constitute 30% to 35% of the retinal thickness in the macular region.8 Studies of chronic experimental glaucoma in monkey eyes have shown a substantial loss of retinal ganglion cells in the zone surrounding the fovea.9,10 Furthermore, a significant association exists between loss of retinal thickness in the posterior pole and visual function.8

The size and anatomical distribution of retinal ganglion cells varies throughout the posterior pole.9,11 Approximately 50% of retinal ganglion cells are located in the macular region 4 to 5 mm from the center of the fovea12 with the peak density occurring 750 to 1100 µm from the foveal center where the cell density may be 4 to 6 cell bodies thick.13 Although cell diameter distribution is variable, a skewed distribution toward larger cell diameters (eg, 14-16 µm) exists in the normal retina, and such cells have been shown to be selectively lost in human and experimental models of glaucoma.1,9,11 Postmortem analysis of enucleated human glaucomatous eyes has demonstrated that a 20% loss of retinal ganglion cells throughout the central 30° of the retina was associated with a 5-dB sensitivity loss with automated perimetry; a 40% loss corresponded to a 10-dB loss in sensitivity.1

Optical coherence tomography (OCT) is a noninvasive, noncontact, transpupillary imaging technology that can image retinal structures in vivo with an axial resolution of 10 to 15 µm.14,15 It provides quantitative, objective, and reproducible assessment of retinal and RNFL

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thickness. Good correlation has been reported between peripapillary RNFL thickness measured by OCT and visual function as well as histological measurements of the nerve fiber layer thickness.

Zeimer et al reported a significant correlation between glaucomatous visual field defects and reductions in macular thickness using a retinal topographer (Retinal Thickness Analyzer; Talia Technology Ltd, Neve Ilan, Israel) based on the principles of slitlamp biomicroscopy. Significant losses in retinal thickness at the posterior pole of up to 34% were reported to occur in patients with early glaucoma (mean corrected pattern standard deviation, approximately 5.5 dB). The purpose of this investigation was to evaluate the correlation between macular thickness and RNFL thickness as measured by OCT in normal eyes and eyes with moderate glaucomatous optic neuropathy.

**METHODS**

Normal (control) and glaucomatous eyes meeting the eligibility criteria were enrolled in this prospective study. Informed consent was obtained from all subjects by means of a consent form approved by the Institutional Review Board for Human Research of the University of Miami School of Medicine, Miami, Fla. All patients underwent complete ophthalmic examination, including slitlamp biomicroscopy, gonioscopy, Goldmann applanation tonometry, dilated stereoscopic examination of the optic disc and fundus, and achromatic automated perimetry.

Control subjects had no history of ocular disease. All had intraocular pressure of 21 mm Hg or less by Goldmann applanation tonometry, normal optic disc appearance based on clinical stereoscopic examination and review of stereo disc photography, and normal perimetry. Absence of glaucomatous optic neuropathy was defined as vertical cup-disc asymmetry of less than 0.2, a cup-disc ratio of less than 0.6, and an intact neuroretinal rim without peripapillary hemorrhages, notches, localized pallor, or RNFL defect. Normal visual field indices were defined as a mean defect and corrected pattern standard deviation within 95% confidence limits and a glaucoma hemifield test result within normal limits.

Glaucomatous optic neuropathy was defined as either cup-disc asymmetry between fellow eyes of greater than 0.2, rim thinning, notching, excavation, or RNFL defect. Patients with glaucoma had glaucomatous optic nerve damage and associated achronic visual field loss in the corresponding hemifield location. Patients with achronic visual field abnormalities had at least 1 confirmatory visual field examination. Eyes with visual acuity of less than 20/40, retinal disease, or unreliable perimetry (greater than 25% fixation losses or false-positive and false-negative rates) were excluded from this investigation.

Optical coherence tomographic imaging (OCT 1; Zeiss-Humphrey Systems, Dublin, Calif) of the macular and peripapillary RNFL was performed in all patients within 6 months of clinical examination; OCT was performed using near-infrared, low-coherence illumination (840 nm) with a tissue resolution of approximately 10 to 17 µm. Image acquisition was performed by one of us (H.B.) and analyzed with version A6.1 software. After pupillary dilation to a minimum diameter of 5 mm, three 360° circular scans with a diameter of 3.4 mm centered on the optic disc were performed. Scan acquisition time was 1.0 second. Each scan consisted of 100 individual A-scan samples evenly distributed along the circle circumference. Mean RNFL thickness was calculated from the values of the 3 scans. Macular thickness measurements were generated using 6 radial scans (each 5.9 mm) centered on the fovea (Figure 1). These scans are processed to produce a topographic map of the macula (Figure 2B). Mean quadrant measurements were generated from the retinal map consisting of sectoral measurements located 0.5 mm to 1.7 mm outside the center of the fovea.

Statistical analysis was performed using JMP software (SAS Institute Inc, Cary, NC). Analysis of variance was used to compare different measures among the groups. Statistical associations among macular thickness values, peripapillary RNFL thickness, and visual function were evaluated using the Pearson correlation coefficient. No adjustments were made for multiple comparisons. P<.05 was considered statistically significant.

**RESULTS**

Fifty-nine eyes of 59 patients (29 normal and 30 glaucomatous) were enrolled (mean ± SD age, 56.7 ± 20.3 years; age range, 20-91 years). All eyes with glaucoma had associated visual field loss (mean ± SD mean defect, −8.4 ± 5.8 dB). Clinical characteristics of the study population are described in Table 1. As illustrated in Table 2, mean macular thickness and mean peripapillary RNFL thickness in glaucomatous eyes were significantly less than mean macular thickness and mean peripapillary RNFL thickness in control subjects. The relationships among visual field defects and RNFL and macular thickness for one case are illustrated in Figure 2.

Correlations between macular and RNFL thickness values were evaluated among a subgroup of 11 similar patients with glaucoma and visual field loss localized to a single hemifield (Table 3). As illustrated in Figure 3, mean macular thickness in the hemifield associated with the field defect (277 ± 28 µm) was significantly less compared with the unaffected hemifield (286 ± 27 µm) (P = .005; paired t test). Mean RNFL thickness was significantly less in the affected hemifield (89 ± 53 µm) compared with the unaffected hemifield (121 ± 39 µm) (P = .009; paired t test). Macular thickness was significantly correlated with RNFL thickness in the posterior segment quadrants associated with the field defect (P < .001; paired t test).
As illustrated in Figure 4, significant correlations were observed between OCT-generated mean macular thickness and visual field mean defect \( (R^2=0.47; P<.001) \) and pattern standard deviation \( (R^2=0.32; P<.001) \). Significant correlations were similarly observed between mean peripapillary RNFL thickness and visual field mean defect \( (R^2=0.45; P<.001) \) and pattern standard deviation \( (R^2=0.35; P<.001) \). Mean macular thickness was sig-
significantly associated with mean RNFL thickness ($R^2 = 0.38$; $P < .001$) (Figure 5).

**COMMENT**

Glaucoma is a complex multifactorial disorder characterized by a typical pattern of optic nerve damage and visual field loss that is usually but not always associated with elevated intraocular pressure. Accepted parameters for monitoring glaucoma include descriptions and photography of the optic disc appearance (eg, cup-disc ratio), measurement of intraocular pressure, and periodic threshold perimetry. Advances in posterior segment imaging technology provide a means for generating structural data useful in monitoring eyes with glaucomatous optic nerve damage. Objective, quantitative measurements of the optic nerve and surrounding RNFL generated with these technologies correlate with known characteristics of optic disc structure and visual function.

The results of this report suggest that macular thickness measurements generated with OCT represent a neglected structural end point for glaucoma. Although glaucoma is an optic nerve disorder, the fundamental defining abnormality is localized at the level of the retinal ganglion cell. Glaucoma is known to cause loss of ganglion cells and their axons, leading to a reduction in the thickness of the RNFL. Macular thickness measurements represent a surrogate indicator of retinal ganglion cell thickness and could prove to have clinical value for glaucoma diagnosis and detection of change. Our results support this hypothesis and illustrate a significant correlation between macular thickness and 2 established indicators of glaucomatous damage: RNFL loss and loss of visual field.

We found significant differences in mean macular thickness between control subjects and patients with moderately advanced glaucoma using direct measurements of retinal thickness generated with OCT. As illustrated in Figure 4, both macular and RNFL thickness assessments were strongly correlated with visual field global indices. The parallel slopes of the regression lines suggest that both parameters should be equally robust discriminators for disease detection. Furthermore, macular thickness and RNFL thickness assessments were significantly associated with each other, suggesting concordance between loss of retinal ganglion cells and their axons. These observations were emphasized in patients with visual field loss confined to a single hemifield who illustrated regional reductions in macular thickness that corresponded topographically to regional reductions in RNFL. Longitudinal studies are necessary to determine whether macular thickness reductions precede RNFL loss or vice versa. For macular thickness measurements to be clinically useful, collection of age-corrected normative data with 95% confidence limits is necessary. Furthermore, to detect glaucomatous progression, statistical criteria are necessary to differentiate test-retest variability from true biological change.

Eyes with visual field loss confined to a single hemifield had a mean difference between the affected and unafflicted macular quadrant thickness of only 9 µm, suggesting that regional macular thickness data may have limitations. A 3.4-mm diameter macular map corresponds to a visual angle of 6° from fixation. Eyes with early visual field defects located far from fixation may have had undetectable ganglion cell loss using a macular map of this diameter. Furthermore, the topographic location of retinal ganglion cell death may have been temporal to the macular quadrant suspected to be associated with the field defect. As illustrated in Figure 2, the inferior macular quadrant was suspected to be associated with the superior field defect; however, perhaps the most significant reduction in macular thickness occurred in the inferior temporal fovea. Finally, although the foveola (diameter approximately 300 to 400 µm) is devoid of ganglion cells, relevant data may have been inadvertently eliminated by neglecting the central 1.0-mm diameter of the fovea.

### Table 2. Optical Coherence Tomography–Generated Thickness Values in 59 Normal and Glaucomatous Eyes

<table>
<thead>
<tr>
<th>Thickness</th>
<th>Normal (n = 29)</th>
<th>Glaucoma (n = 30)</th>
<th>$P$ Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macular thickness</td>
<td>304 ± 15 (276-338)</td>
<td>278 ± 24 (224-347)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Retinal nerve fiber layer thickness</td>
<td>140 ± 14 (121-168)</td>
<td>91 ± 31 (30-160)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Analysis of variance.

### Table 3. Optical Coherence Tomography–Generated Thickness Values in 11 Eyes With Visual Field Defects Confined to a Single Hemifield

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Mean Defect, dB</th>
<th>Macular Thickness, µm</th>
<th>Retinal Nerve Fiber Layer Thickness, µm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Affected Hemifield</td>
<td>Unaffected Hemifield</td>
</tr>
<tr>
<td>1</td>
<td>−7.93</td>
<td>282</td>
<td>297</td>
</tr>
<tr>
<td>2</td>
<td>−9.34</td>
<td>245</td>
<td>249</td>
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<tr>
<td>3</td>
<td>−1.82</td>
<td>298</td>
<td>323</td>
</tr>
<tr>
<td>4</td>
<td>−1.40</td>
<td>288</td>
<td>284</td>
</tr>
<tr>
<td>5</td>
<td>−3.88</td>
<td>267</td>
<td>271</td>
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<td>6</td>
<td>−2.64</td>
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<td>281</td>
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<td>265</td>
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<tr>
<td>8</td>
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<td>245</td>
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<td>10</td>
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<td>279</td>
<td>285</td>
</tr>
<tr>
<td>11</td>
<td>−9.21</td>
<td>259</td>
<td>272</td>
</tr>
</tbody>
</table>
the macular map thought to consist largely of photoreceptor cells. Nevertheless, a statistically significant reduction in thickness was identified in the macular quadrant predicted to be associated with the field defect. Advances in axial resolution of this technology, and software designed to extract data from more pertinent topographic areas, would be expected to improve detection of retinal ganglion cell loss in glaucoma.

Based on the principle of low-coherence interferometry, OCT provides high-resolution, cross-sectional imaging of the retina and the RNFL. A high level of correlation between OCT-generated RNFL thickness and visual function has been reported by several authors. As presently configured, OCT employs 100 A-scans with an axial resolution of 10 to 20 µm, which limits the ability to visualize and measure the retinal ganglion cell layer. A modification of this technology that was recently approved by the Food and Drug Administration employs 512 A-scans and has an axial resolution of approximately 8 µm with no need for pupillary dilation. This modification may provide a potential means to directly visualize and measure the retinal ganglion cell layer. Emerging therapeutic strategies such as neuroprotection emphasize the need to identify and measure such cells for glaucoma diagnosis and monitoring.

There is considerable evidence to support the relationship between RNFL loss and reductions in visual function using various posterior segment imaging technologies. The discriminating power of these instruments is limited by the wide distribution of normative RNFL data among the general population as well as technological assumptions. It remains unclear whether macular thickness loss may be a more robust indicator of early glaucomatous damage. Furthermore, as with RNFL thickness assessments, longitudinal studies are necessary to validate their ability to detect glaucomatous progression. It is important to emphasize that macular thickness measurements have limited use for monitoring glaucoma in eyes with macular comorbidity. Thus, eyes with diabetic or age-related maculopathy are not candidates for monitoring macular thickness changes as a strategy for glaucoma diagnosis or detection of glaucomatous progression.

In conclusion, macular thickness changes are well correlated with changes in visual function and RNFL structure in glaucoma and may represent a surrogate indicator of retinal ganglion cell loss. Macular thickness measurements with OCT may provide a new approach for the detection and monitoring of glaucomatous damage.
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REFERENCES


