

# The Literature

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## DETECTION OF PROGRESSIVE RETINAL NERVE FIBER LAYER THICKNESS LOSS WITH OPTICAL COHERENCE TOMOGRAPHY USING 4 CRITERIA FOR FUNCTIONAL PROGRESSION

*Grewal DS, Sehi M, Paauw J, et al<sup>1</sup>*

### ABSTRACT SUMMARY

Grewal et al compared the rates of retinal nerve fiber layer (RNFL) thickness loss using optical coherence tomography (OCT) in glaucomatous eyes with functional progression, glaucomatous eyes without functional progression, and normal controls. Functional progression was defined by Early Manifest Glaucoma Trial criteria, visual field index, pointwise linear regression with the Progressor analysis (Medisoft Ltd.), and the three-omitting method (pointwise linear regression with the Progressor showing progression with two additional visual field tests confirming progression).

A total of 76 eyes of 38 patients were included, of which 46 eyes were glaucomatous, and 30 eyes were controls. All patients underwent a baseline examination consisting of slit-lamp biomicroscopy, gonioscopy, Goldmann applanation tonometry, ultrasound pachymetry, dilated stereoscopic examination, photography of the optic disc, standard automated perimetry (SAP), and OCT imaging. SAP and OCT imaging were performed at 6-month intervals in glaucomatous eyes. OCT imaging was performed on an annual basis in normal subjects. The mean follow-up was 44.2 months  $\pm$  4.4 (range, 36-48 months). At baseline, no difference in the thickness of the RNFL was found between the patients with progressing and nonprogressing glaucoma.

Functional eyes with progressing disease showed a significantly greater annual rate of average RNFL loss compared with eyes with nonprogressing disease using the Progressor ( $-1.0 \pm 1.3$  vs  $0.02 \pm 1.6$ ), visual field index ( $-2.1 \pm 1.1$  vs  $-0.002 \pm 1.4$ ), and the three-omitting method ( $-2.2 \pm 0.2$  vs  $-0.1 \pm 1.5$ ). The mean rate of change of average and superior RNFL thickness was similar in the nonprogressing and control eyes. Furthermore, numerous clinical parameters were significantly associated with the rate of RNFL thickness atrophy, including mean IOP, peak IOP, age, baseline central corneal thick-

"There is currently no consensus among clinicians or investigators as to the best method for defining glaucomatous visual field progression."

ness, disc hemorrhage, exfoliation, baseline SAP mean deviation, and pattern standard deviation.

### DISCUSSION

#### What factors affect the accuracy of RNFL thickness measurements by OCT?

Images that are poorly focused or characterized by weak or variable signal strength should be excluded.<sup>2-4</sup> For each unit decrease in signal strength, the average RNFL thickness is reduced by 2  $\mu$ m.<sup>5</sup> Eye movement, media opacity, axial length, and failure of the RNFL segmentation algorithm will also affect the quality of the scan.<sup>3,5-9</sup> Finally, caution should be used when comparing OCT scans from different devices. The variability between instruments has been demonstrated to exceed the inter-operator variability of two well-trained individuals on the same device.<sup>3</sup>

#### How is glaucomatous visual field progression defined, and how do the results of this study affect assessing the progression of glaucoma?

There is currently no consensus among clinicians or investigators as to the best method for defining glaucomatous visual field progression. In this study, four methods were used to judge progression. Although the rate of progression varied widely (from 4% to 24%) depending on the method chosen, all eyes showing visual field progression had significantly higher rates of RNFL loss compared to eyes with nonprogressing disease. This correlation between structural changes and functional loss provides support for complementing perimetry with imaging to improve the identification of glaucomatous progression.

## STRUCTURE-FUNCTION RELATIONSHIP BETWEEN FDF, FDT, SAP, AND SCANNING LASER OPHTHALMOSCOPY IN GLAUCOMA PATIENTS

Lamparter J, Russell R, Schulze A, et al<sup>10</sup>

### ABSTRACT SUMMARY

Lamparter et al examined the structure-function relationship between flicker-defined form perimetry (FDF), frequency-doubling technology perimetry (FDT), and standard automated perimetry (SAP), with confocal scanning laser ophthalmoscopy (CSLO) in patients with early (n = 26) or moderate to advanced glaucoma (n = 50). Structure-function relationships between global and sectoral CSLO parameters and sensitivity (ie, rim area, rim volume, mean retinal nerve fiber layer thickness, and cup-to-disc area ratio in each of the quadrants) were calculated using Spearman's rank correlation and linear regression.

FDF perimetry showed the strongest structure-function relationship followed by FDT, and then SAP, which was associated with the weakest correlation and the fewest statistically significant results. Sector-by-sector correlation coefficients were largest in magnitude in the superotemporal and inferotemporal sectors for all three perimetric techniques, with FDF demonstrating the strongest correlation. The weakest correlations were found in the superonasal and nasal sectors. The majority of significant correlation coefficients in early glaucoma subjects were FDF, followed by FDT, and finally SAP.

### DISCUSSION

#### What is FDF?

FDF uses a relatively new stimulus specifically designed for the detection of early glaucomatous loss.<sup>11-13</sup> Randomly positioned stimuli of black-and-white dots flicker at high temporal frequency, reversing their polarity without changing their positions. At high temporal frequencies, this is perceived as an illusory circular edge contour, appearing as a gray patch against the mean luminance background. FDF and FDT are designed to detect early glaucomatous damage by their preferential stimulation of magnocellular M cells.<sup>14,15</sup> The exact mechanism by which these tests are able to resolve early glaucomatous damage remains somewhat controversial, and a more thorough understanding of the underlying processes behind this phenomenon is needed before establishing a cause-and-effect relationship.

#### How do these results compare to prior studies?

No previous studies have examined FDF with structural progression in glaucomatous patients. In terms of SAP, Danesh-Meyer et al found the strongest correla-

tion between structure and function in the inferior/inferotemporal sectors and a weaker correlation in the superior sectors.<sup>16</sup> Multiple studies have examined the correlation between structure and function with CSLO and FDT; the strongest correlation has been found in the temporal sectors when compared to nasal counterparts.<sup>17-21</sup> Miglior et al found significant correlation in all sectors, except nasally, which is similar to this study by Lamparter et al.<sup>21</sup>

#### What is the significance of this study?

SAP remains the gold standard for the functional assessment of glaucoma. As more highly refined tools have been developed to assess eyes for structural changes in glaucoma, the relationship and concordance of structural damage with functional deficiency are becoming more apparent. Both FDF and FDT are selective perimetric techniques designed to detect early glaucoma. This study highlights a higher correlation between structure and function with FDF when compared to FDT and SAP. Further study is warranted to confirm these results and to determine the clinical significance of the findings.

## THE STRUCTURE AND FUNCTION RELATIONSHIP IN GLAUCOMA: IMPLICATIONS FOR DETECTION OF PROGRESSION AND MEASUREMENTS OF CHANGE

Medeiros FA, Zangwill LM, Bowd C, et al<sup>22</sup>

### ABSTRACT SUMMARY

Medeiros et al evaluated the relationship between estimated retinal ganglion cell (RGC) counts with changes in mean deviation by standard automated perimetry (SAP) and retinal nerve fiber layer (RNFL) thickness by spectral domain-optical coherence tomography. Subjects included eyes with glaucomatous visual field loss (n = 122), glaucomatous optic neuropathy without visual field loss (n = 80), ocular hypertension (n = 98), and healthy controls (n = 97). Estimates of RGC counts were made from a previously described method from a combination of RNFL thickness and SAP.

The results demonstrated a nonlinear relationship between SAP mean deviation (MD) and estimated RGC counts. The same amount of RGC loss corresponded to different degrees of visual field loss depending on the severity of disease. In earlier stages of glaucoma, large changes in estimated RGC counts were associated with small changes in SAP MD. In contrast, at later stages of glaucomatous damage, small changes in RGC counts were associated with large changes in SAP MD. For

example, for an eye with 1,020,000 RGCs (median value in healthy eyes), losing 10,000 RGCs resulted in only a 0.04-dB change in SAP MD. For an eye with only 281,000 RGCs, a similar loss of 10,000 RGCs resulted in a 0.47-dB change in SAP MD.

In contrast to SAP MD, RNFL thickness demonstrated a linear relationship with RGC counts throughout the majority of the spectrum of disease. For eyes with greater than 500,000 RGCs, the RNFL thickness decreased by 0.5  $\mu\text{m}$  for every 10,000 RGCs lost. In eyes with less than 500,000 RGCs, the rate of loss plateaued rapidly, and further loss of RGCs resulted in a lower rate of thinning. Eyes with an estimated RGC count of 200,000 or below demonstrated virtually no further thinning of measured RNFL. This RGC count approximately corresponded to an RNFL thickness of 55  $\mu\text{m}$ .

## DISCUSSION

**What are the implications of these findings on judging rates of progression in glaucomatous eyes?**

Rates of progression depend on disease severity at baseline. At early stages of glaucoma, there is a linear relationship between RGC loss and RNFL thinning. This same amount of RGC loss, however, is associated with a relatively small impact on SAP MD. Therefore, incorrectly assuming a linear rate of perimetric progression in early glaucoma would underestimate the risk of significant long-term visual disability. In other words, visual field stability in early stages of disease should not be misinterpreted as predictive of long-term safety if structural damage is occurring over time. Changes in RNFL thickness are more useful and indicate progression in earlier stages of glaucoma.

More advanced glaucoma is characterized by smaller ganglion cell reserves, and therefore, larger changes in SAP MD result in the same amount of RGC loss. In end-stage disease, RNFL thickness is a less meaningful metric due to the demonstrated plateau effect with extensive damage.

## Why does RNFL thickness plateau with advanced disease?

This study found a fairly constant decrease of 0.5  $\mu\text{m}$  in RNFL thickness for every 10,000 RGCs lost with RGC counts of greater than 500,000. Below this amount, the RNFL thickness measurements plateau, rarely falling below 50  $\mu\text{m}$  and never below 40  $\mu\text{m}$ . This is speculated to be due to the presence of nonneural or glial tissue as well as the limitations of the instruments used to measure RNFL thickness.<sup>23-25</sup> For example, in one model, blood vessels were estimated to contribute 13% of the average RNFL thickness, whereas this percentage increased significantly with significant RNFL thinning.<sup>24</sup> Higher-resolution imaging modalities may help mitigate some of these limitations. ■

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