Early glaucoma involves both deep local, and shallow widespread, retinal nerve fiber damage of the macular region.

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Running Head: Circumpapillary Glaucomatous Defects

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ABSTRACT

Purpose: To better understand the nature of early glaucomatous damage of the macula by comparing the results from 10-2 visual fields, optical coherence tomography (OCT) macular cube scans, and OCT circumpapillary circle scans.

Methods: One eye of 66 glaucoma patients or suspects, with a mean deviation (MD) on the 24-2 VF test of better than -6 dB, was prospectively tested with 10-2 VFs and OCT macular cube and circumpapillary circle scans. Thickness and probability maps of the retinal ganglion cell plus inner plexiform (RGC+) layers were generated. A hemifield was considered abnormal if both the macular RGC+ and the 10-2 probability plots were abnormal (cluster criteria). The thickness plots of the circumpapillary retinal nerve fiber layer (RNFL) were analyzed in the context of a model that predicted the region of the disc associated with macular damage.

Results: 27 hemifields (20 eyes) had abnormal 10-2 and RGC+ probability plots: 7 in upper VF/inferior retina; 6 in lower VF/superior retina; and 7 in both hemifields. Both shallow widespread and deep local thinning of the circumpapillary RNFL were observed. The local defects were more common and closer to fixation in the upper VF/inferior retina as predicted.

Conclusions: A model of glaucomatous damage of the macula predicted the location of both the widespread and local defects in the temporal and inferior disc quadrants. OCT scans of the circumpapillary RNFL and the macular RGC+ layer can aid in the identification of these defects and help in the interpretation of 24-2 and 10-2 visual field tests.
Over 30% of the retinal ganglion cells (RGCs) are within the macular region, defined here as the central ±8°. While it is clear that early, even initial, glaucomatous damage can involve these RGCs and the macula, the nature of this damage is incompletely understood. We recently proposed a model based upon visual field (VF) and optical coherence tomography (OCT) data to explain some of the key aspects of macular damage.

According to this model, schematized in Figure 1, the temporal quadrant of the disc contains the axons from RGCs in the gray region, which includes the RGCs of the superior macula and some of the RGCs of the inferior macula. However, most of the inferior RGCs are within the purple borders and their axons project largely to the inferior quadrant of the disc. To relate this structural map to VF defects, we made the commonly accepted assumption that glaucomatous defects are more likely to occur, and tend to be more severe, in the superior and inferior quadrants of the disc (orange arcs on disc in Fig. 1), than in the temporal quadrant. Thus, the RGCs within the region of the macula shown in gray in Figure 1 are less vulnerable to glaucomatous damage relative to those outside this region. The RGCs just outside this gray region, including most of the lower macula, project to the superior and inferior quadrants and are at greater risk of glaucomatous damage. Of course, the boundaries between more or less vulnerable regions are not as abrupt as shown. Further, there are individual differences in the mapping of RGCs to the optic disc, which may in part depend on the degree of elevation of the position of the disc relative to the fovea (see Fig. 16 in ref. 12).

This model provides an explanation for why macular defects in the upper VF tend to be more severe and closer to fixation than those in the lower VF. Local RNFL bundle defects in the temporal part of the inferior quadrant produce focal, arcuate-like VF defects close to fixation in the upper VF. However, the same focal defect in the temporal portion of the superior disc leads to an arcuate-like VF defect of the lower VF that is further from fixation and largely outside the macula. Consistent with the model, VF arcuate defects occurring largely within the macula (i.e. within ±8°), are typically seen in the upper VF (inferior retina). In addition, the model predicts the pattern of VF preserved in very advanced glaucoma. However, the model still requires refinement.

While the model was designed to explain the location of relatively local RNFL bundle defects and their associate VF locations, there is evidence that, more widespread or diffuse
damage of the macula also exists, although there is some debate on this point.\textsuperscript{17-23} One purpose of the present study was to test the hypothesis that all macular damage in patients with mild glaucomatous damage is due largely to relatively local RNFL damage at the optic disc. More generally, the purpose here was to better understand the nature of early (mild) glaucomatous damage of the macula, especially its manifestation as damage at the optic disc as seen in circumpapillary RNFL thinning. We excluded eyes with mean deviations (MD) worse than -6 dB on 24-2 VFs in order to focus on early damage. In addition, to avoid false positives, eyes selected for OCT RNFL analysis had at least one hemifield that was abnormal on both the 10-2 VF and the OCT macular cube scan.

**METHODS**

**Subjects**

One eye of 66 open-angle glaucoma suspects and patients was prospectively tested with fdOCT and 10-2 VFs. Patients were $\leq$75 years of age ($53.8 \pm 15.3$ years). Eyes were included if they had glaucomatous optic neuropathy (GON) on fundus examination and a mean deviation (MD) of -6 dB or better on the 24-2 VF (Humphrey VF Analyzer; Carl Zeiss Meditec, Inc, Dublin, CA). GON was defined based on stereophotography evaluation by glaucoma specialists using the following criteria: focal or diffuse neuroretinal rim thinning, focal or diffuse RNFL loss or an inter-eye vertical cup-to-disc ratio asymmetry $>$0.2 not explained by differences in disc size. All eyes had open angle glaucoma based on the definitions above and the presence of open angles during gonioscopic examination. All patients had fdOCT macular cube and circular disc scans, as well as 10-2 and 24-2 VFs within 6 months. Twenty-eight (42.4\%) of the eyes were classified as high-tension glaucoma (HTG) or were HTG suspects, while 38 (57.6\%) were classified as normal-tension glaucoma (NTG) or were NTG suspects. NTG was defined based on the presence of all known untreated intraocular pressure measurements lower than 20 mmHg. All included eyes had best corrected visual acuity of 20/40 or better and eyes with other conditions likely to affect the VF results (e.g. cataract, corneal opacity, neuroophthalmologic or retinal diseases) were excluded. Fifty-two healthy eyes of 52 individuals (age $52.7 \pm 7.6$ years) served as controls for the fdOCT cube scans.\textsuperscript{11} They had normal fundus examinations and normal 24-2 VF tests.
SAP

The 10-2 VFs were obtained with the SITA-standard protocol and all met reliability criteria (fixation losses ≤33%, false positives ≤15% and false negatives ≤20%). Each hemifield was classified separately and considered abnormal if at least 3 contiguous test points (at 5%, 2%, 2% or 5%, 5%, 1%) respecting the horizontal midline were present on either total deviation (TD) or pattern deviation (PD) probability plots.

fdOCT

All patients had cube scans of the macula (6 mm by 6 mm, 128 horizontal B-scans with 512 A-scans each) and all but one had a circumpapillary circle scan (1.7 mm radius, 1024 A-scans with at least 16 overlapping averages; 3D-OCT 1000/2000, Topcon Medical Systems, Inc., Paramus, NJ). The combined RGC and inner plexiform layers (RGC+) of the OCT scans were segmented using a computer-assisted manual segmentation technique. Figure 2A illustrates the segmentation of the center scan from a macular cube scan.

RGC+ thickness and probability maps: For each of the 20 eyes, RGC+ thickness maps were produced from the segmented OCT cube scans (Fig. 2B, upper left). Probability maps were obtained from the RGC+ thickness maps after a point-by-point comparison to control values (lower panel in Fig. 2B).

OCT RGC+ classification: In order to classify the macular scans and 10-2 VFs in a similar manner, RGC+ thickness maps (Fig. 2B, left panel) were down-sampled into an 8 by 8 grid (64 locations) and coded for probability based upon control data (Fig. 2B, right). A hemifield was considered abnormal if at least 3 contiguous abnormal squares (at 2%, 2%, 1%) respecting the horizontal midline were present. By this criterion, 5 of the 108 hemifields of the control eyes were abnormal, yielding a false positive rate of 4.6%.

Classification scheme: To help ensure we are dealing with real defects, i.e., to avoid false positives, only the hemifields abnormal on both the VF and OCT RGC+ maps were included in subsequent analyses. This resulted in 27 abnormal hemifields and 20 eyes. We divided
the 20 eyes into three groups (Upper, Lower, Both) depending upon whether the upper VF (inferior retina), lower VF (superior retina), or both hemifields were abnormal using the cluster criteria described above.

*Circumpapillary OCT analyses:* The circumpapillary RNFL thickness was obtained after correction of the segmented RNFL on the circle scan (upper panel in Fig. 3A) and plotted as the black curve in the lower panel of Fig. 3A. Notice that the temporal quadrant is shown in the center. That is, this is a NSTIN plot, not a TSNIT plot.

**Prediction from the model**

To relate the RNFL plots in Fig. 3A (black curve) to the model, we needed to specify the boundaries of the macular RGCs’ input to the disc. The boundaries chosen are shown in Fig. 3C. The upper boundary was set at 45°, the boundary of the temporal and superior quadrants of the disc. The boundary between the superior and inferior macular region was set at -12° based upon our tracing of RNFL bundles (Fig. 15 in ref 12). Finally, the inferior border was set at 69° to include the region, called the macular vulnerability zone (MVZ),\textsuperscript{11,12} associated with macular defects of the upper VF and to have the same width (57°) as the superior region at the disc. As mentioned above, individuals vary\textsuperscript{12,14,15} and boundaries are not sharp. In any case, the main conclusions here do not depend upon these exact values.

The boundaries of the model are superimposed on the RNFL plots as in Fig. 3A. Thus, according to the model, for upper macular (±8°) VF defects, there should be abnormal thinning within the region bordered by the blue vertical lines and shown as the horizontal blue line with arrows. Likewise, for lower macular (±8°) VF defects, we should see abnormal thinning within the region bordered by the red vertical lines and shown as the horizontal red line with arrows.

**RESULTS**

In 20 of the 66 eyes, at least one hemifield was abnormal on both OCT and 10-2 VF tests. Both hemifields were abnormal in 7 of these 20 eyes, while only the upper VF (inferior
retina) was abnormal in 7 eyes and only the lower VF (superior retina) in 6 eyes for a total
of 27 abnormal hemifields. Table 1 contains some key information about these 20 eyes.

**Group data**

Figure 4 shows average results for the three groups with abnormalities only in the upper,
only in the lower or in both hemifields. Results are presented as right eyes. The hemifield of
interest is enclosed within a colored rectangle, blue for upper VF/inferior retina and red for
lower VF/superior retina.

The leftmost panels show the average 10-2 results (field view) as TD (dB) values in
pseudo-color. The points of the 10-2 were morphed to take the displacement of the RGCs
near the fovea into consideration, as previously described. The pattern of defects
differed for the Upper and Lower VF groups. The average upper VF defects (Fig. 4A) were
deeper (i.e., more negative TD values) and closer to fixation than the lower VF defects (Fig.
4B). The eyes with both hemifields classified as abnormal (Fig. 4C) showed less deep VF
defects in the upper VF than did the Upper group.

The middle panels of Fig. 4 show the RGC+ thickness maps (see Fig. 2B) in retinal view.
The RGC+ results are in agreement with the 10-2 VF results. The RGC+ thinning in the
lower retina of the Upper group is more extreme, and closer to fixation than the RGC+
thinning in the upper retina of the Lower or Both groups.

The results from the circumpapillary scans are of particular interest for this study. The
rightmost panels of Figure 4 show the average circumpapillary RNFL plot. The Upper VF
group shows a relatively local RNFL defect with a thinning within the region between the
blue vertical lines as predicted by the model (Figs. 1 and 3). The peak of this thinning is
near the border of the temporal and inferior quadrants of the disc. On the other hand, the
average RNFL for the eyes with both hemifields abnormal shows a more widespread and
shallower thinning throughout the region between the red and blue vertical lines, that is,
the region associated with the macula by the model. The RNFL thinning in the Lower VF
group is subtler. However, the RNFL thickness fell below the 95% confidence limit (yellow
region) in the region around the border of the temporal and superior quadrants of the disc.
This is the region expected from the model to be associated with the defects seen on the
10-2 VF and RGC+ map for the Lower VF group.
**Individual data**

The data for each of the 20 eyes is presented in Figures 5-7. All results are presented as if from right eyes. The format for each eye in Figures 5-7 is the same. The upper row contains the TD probability plot (left) and the TD values (right) for the 10-2 VF test, both in field view. For the latter, the locations of the test points were morphed as above. The middle two panels are the total thickness and probability maps for the RGC+ layer presented in retinal view. The bottom row has the RNFL thickness (black curve) for the circumpapillary scan along with the confidence limits for the healthy controls from the OCT machine.

**Upper VF abnormal:** Figure 5 contains the results for the eyes in which only the Upper VF (inferior retina) was abnormal; they are ordered by mean TD in the upper hemifield of the 10-2 VF test from largest (P1: -16.4 dB) to smallest (P7: -1.4 dB) loss. The blue rectangle indicates the region of interest. The pattern of results was extremely similar in 6 of these 7 eyes (P1-P6) and similar to the overall average for this group in Fig. 4A. First, the upper hemifield of the 10-2 VF showed relatively severe local damage with regions of loss of -8 dB or more. In fact, in P1 through P4 the local loss exceeded -27 dB. Second, the RGC+ thickness and probability maps (the panels on second row) showed damage largely, if not entirely, in the inferior retina (upper VF). Furthermore, the RGC+ thinning was extreme in at least part of the macular region, as seen on the thickness and probability maps.

The RNFL thickness plots (third row) for P1-P6 showed local thinning in the region predicted by the model (i.e., between the blue vertical lines). In fact, this thinning was relatively extreme (deep), extending well into the red (1%) region on the RNFL plot. On the OCT scans, it appears as a nearly complete thinning of the RNFL in all 6 of these eyes. This region of extreme thinning is illustrated in the case of P1 in Figure 3A, where it is marked with white and black arrows. Two more examples, P2 and P4, are shown in Figure 8A,B. The point of maximum thinning tended to be close to the border of the temporal (T) and inferior (I) quadrants in these 6 eyes. Further, these defects were relatively local; the RNFL thickness was in the normal range over portions of the temporal region of the disc associated with the macula. We will call these “deep local defects” of the macular RNFL.
P7 presented with a very different pattern of results. In particular, the VF and OCT results suggest a milder and more widespread loss in both upper and lower hemifields. The average TD of the upper VF was only -1.35 dB and was the same as that of the lower VF. Further, the probability and thickness maps show changes of approximately the same degree in both hemispheres. Finally, the RNFL is borderline abnormal (yellow zone) throughout the 114° region (from +45° to -69° in Fig. 3C) predicted by the model, as well as beyond the border of the model in the inferior quadrant. It is possible that this eye is a false positive, i.e., it does not have glaucomatous damage. However, we think it more likely that damage in the lower VF/superior retina was missed on the VF, but is seen clearly on the RGC+ maps. In fact, as will be seen below, the pattern of RNFL thinning is very similar to that seen for the Both group, where both hemifields were categorized as abnormal.

Lower VF Abnormal: Figure 6 contains the results for the eyes in which only the Lower VF was abnormal; they are ordered by the mean of the 10-2 TD values in the lower hemifield from largest (P8: -5.1 dB) to smallest (P13: -0.7 dB) loss. The red rectangle indicates the region of interest. Of the 6 eyes, only P9 showed deep local damage similar to that seen in P1-P6 of the Upper VF group. In particular, P9’s 10-2 VF showed local TD values as large as -19 dB and the RGC+ maps indicated a deep loss of the RGC layer largely in one hemifield. The RNFL plot has a marked thinning on the border of the temporal and superior quadrants, which can be seen in Figure 8C (white arrow).

The pattern of results in the other 5 eyes was markedly different and was more similar to the average results for this group in Fig. 4B. First, the VF defects were milder. The mean TD for lower hemifield of all 6 eyes was -2.6 dB compared to -7.2 dB for the 7 upper hemifields in the Upper group (Table 1). The defects were also shallower than those in the Upper group. Only one point in all 5 lower VFs was less than -7 dB. Second, while the RGC+ thickness and probability maps showed clear thinning in the superior retina, in general, this thinning was not as extreme as that seen in Fig. 5 for the affected hemifield of the Upper group.

Third, while the RNFL thickness plots (third row) showed local thinning in the region predicted by the model (i.e., between the red vertical lines), the RNFL thinning in this region was less obvious than for the Upper group. Although it involved the red (1%) region
in the case of P8 and P9, it was borderline abnormal in P11 and P13, and in the normal range in P10 and 12. However, the VF and OCT data taken together suggest shallow damage in these 5 eyes. This damage is apparent on the RGC+ maps, but can be subtle, or even missed, on the circumpapillary RNFL plot. Further evidence that the RNFL plot may miss subtle damage in the temporal quadrant can be seen in the case of P12 in Fig. 6, where the gray curve is the RNFL thickness for the patient’s other eye, with better vision. This other eye had a better VF and a clearly thicker RNFL in the macular region between the red vertical lines. This supports the view that the temporal RNFL thickness of the affected eye of P12 had been diminished, but the thinning did not fall below the normal limits. In addition, P9, P10, and P13 had mfVEP tests that corroborated the macular damage suggested by the 10-2 and RGC+ maps. In the case of P13, the mfVEP showed both upper and lower macular abnormalities. The mfVEP results, together with the RGC+ map and RNFL plot, suggest that this eye had damage throughout the macula region, like the eyes in the Both group discussed next.

Both hemifields abnormal: Figure 7 contains the results for the eyes in the Both hemifield group ordered by the overall mean TD loss (MD) from largest (P14: -6.8 dB) to smallest (P20: -2.2 dB). Except for P14, the mean TD values of the upper and lower 10-2 VFs were within 2 dB of each other (Table 1). The mean TD values of the upper and lower VFs were -4.8 dB (upper) vs. -3.6 dB (lower) with P14 and -3.8 dB (upper) and -3.6 dB (lower) without P14. Only the upper 10-2 VF of P14 showed the kind of deep 10-2 defect seen in the upper 10-2 VF of P1-P4 and in the lower VF of P9. In general, the 10-2 VFs and the RGC+ maps argue for shallower and more widespread damage of the entire macular region than seen in the Upper group of eyes.

The RNFL plots are in agreement. All 7 eyes show an abnormal thinning of the RNFL throughout the 114° region associated with the macula according to the model, i.e., throughout the regions within the blue and red vertical lines. The abnormal RNFL thinning extended beyond this region into the inferior and/or superior quadrants. The thinning outside the macula region ranged from relatively deep (red region) to borderline (border of yellow and green regions). In Fig. 8, P17 (panel D) is an example of the former and P18 (panel E) the latter. In general, the RNFL can be said to exhibit widespread shallow damage...
in the portion of the disc associated with the macula, although there were inferior RNFL regions of relatively deep damage in P14, P17 and P19. However, none of the 7 inferior macular regions showed a deep defect at the border of the temporal and inferior quadrants, as seen in the Upper group. That is, the damage in these eyes cannot be described simply as a combination of the damage seen in the Upper and Lower groups.

**Macular damage and high- versus normal-tension glaucoma**

Patients with NTG were no more likely to have macular damage, as defined here, than were patients with HTG. Of the 20 eyes with macular damage, 9 or 45% had NTG, while 57.6% (38) of the 66 eyes in the study had NTG. However, 8 of the 13 eyes with only one abnormal hemifield had NTG, while only 1 of the 7 with both hemifields affected had NTG. This difference is even more extreme if we assume, as argued above, that both hemifields of P7 and P13 were abnormal. With these included in the Both group, 8 of the 11 eyes (72.7%) with one hemifield affected had NTG, and 8 of the 9 (88.9%) with both hemifields affected had HTG.

**DISCUSSION**

The general purpose of this study was to better understand the nature of early glaucomatous damage of the macula, especially as it manifests in circumpapillary RNFL thickness plots. To restrict our study to early glaucoma, only eyes with a MD better than -6 dB on the 24-2 VF test were included. In fact, all 20 eyes had a 24-2 MD better than -5 dB. Further, to avoid false positives, we included only the 20 eyes that were abnormal on both the 10-2 VF test and RGC+ probability plots, as defined by cluster criteria mentioned above. The results argue that early glaucomatous damage involves both shallow widespread, as well as deep local, thinning of the circumpapillary RNFL. In addition, they suggest that the model of macular damage needs further elaboration.

**Relatively deep local RNFL damage**

In 7 eyes, the circumpapillary RNFL contained a relatively local macular region with severe thinning of the RNFL. This thinning included the region that the model associates with the macula. We called these “deep local defects” of the macula. Six of these eyes (P1-P6) had
upper 10-2 VF defects and one (P9) a lower 10-2 VF defect. The 6 with upper VF defects had marked RNFL thinning in the inferior macular region near the border of the temporal and inferior quadrants, which included the inferior region of the temporal quadrant and the temporal portion of the inferior quadrant. This is the region of the disc we have previously associated with arcuate-like defects within the macula.\textsuperscript{10-12} The point of maximal thinning occurs in and relatively narrow range between about -38° and -65° using the reference system in Figure 3.\textsuperscript{10} We have referred to this region as the “macular vulnerability zone (MVZ)”.\textsuperscript{12} The associated RGCs fall in the region within the purple borders in Figure 1. Figures 3 and 8 shows the RNFL scans of 3 examples, P1, P2 and P4, of patients with maximum thinning in the MVZ. Notice that there is a near total thinning; a similar pattern was seen in P3, P5 and P6.

In the present study, only one eye, P9 (Fig. 6), showed an analogous lower VF defect, with a deep RNFL thinning maximal at the border of the temporal and superior quadrants (Figs. 6 and 8). Consistent with the model, there was an arcuate defect that spanned both the 10-2 and 24-2 VFs, and was further from fixation than the local defects in the upper VF/lower retina seen in P1-P6.

The presence of deep, local macular VF defects in early glaucoma has been well-documented in previous studies\textsuperscript{2-5,9,10} and associated with severe thinning of the circumpapillary RNFL.\textsuperscript{10} Consistent with our findings, these defects are more prevalent in the upper macular VF, where they are closer to fixation and deeper than those in the lower macular VF.\textsuperscript{4,5,9,10,16,27} The literature also suggests that these defects are relatively more common in eyes with NTG.\textsuperscript{27-32} In the present study, the sample (7 eyes) with only deep local defects was small, but the trend is in the same direction, 13.1% of the NTG eyes versus 7.1% of the HTG eyes.

Relatively shallow widespread RNFL damage

The results for the Both group supply the best evidence for relatively shallow and widespread RGC+ and RNFL damage of the macula. All 7 of these eyes showed widespread loss of 10-2 sensitivity, thinning of the macular RGC+ layer and thinning of the RNFL throughout the region that the model associated with the macula. In addition, P7 from the Upper group and P13 from the Lower group probably represent milder versions of shallow
widespread damage. The shallow widespread damage can include most, or all, of the disc as in P13 and P17 (Fig. 8D,F), or only the temporal half of the disc as seen in P18 (Fig. 8E).

P14, P15 and P19 show a combination of shallow widespread RNFL thinning of the macular region of the disc combined with more localized deeper RNFL defects; the latter appeared as deep defects on the 24-2 TD.

Because miosis and cataracts can produce widespread loss in visual sensitivity across the VF, the prevalence and nature of widespread or diffuse VF damage have been debated. In general, however, the literature indicates that widespread loss can occur. For example, Henson et al argued that there is often a widespread component to early glaucomatous damage seen on 24-2 VFs, although this is subtle (≤ 2dB) and typically associated with deeper, more localized VF defects. Our evidence for widespread damage of the macula rests largely on OCT findings, which are relatively unaffected by miosis or cataracts. Interestingly, all but one of our patients with widespread macular damage had HTG, consistent with the old view that diffuse loss is more commonly seen in cases with high IOP.

Implications for the model of macular damage

Our model in Figure 1 was proposed to describe glaucomatous damage of the macula. It is a model of healthy anatomy, as well as a model of the location of glaucomatous damage. In other words, it has anatomical assumptions about the map between the location of macular RGCs and locations at the disc, as well as assumptions about the relative vulnerability of different parts of the disc to glaucomatous damage. The present results support the anatomical assumptions. In general, the thinning of the circumpapillary RNFL associated with VF and RGC macular abnormalities occurred in the region predicted by the model. However, the assumptions about relative vulnerability of different regions of the disc need elaborating.

The schematic model in Figure 1 presents a simplified picture of regions that are more or less vulnerable to relatively local glaucomatous damage. First, concerning relatively local damage, the MVZ (approximately -38° to -65°) is associated with the inferior portion of the macula, while the equivalent region (38° to 65°) located at the border of the temporal and superior quadrants of the disc is largely associated with the regions of the retina lying
outside the macula. In addition, the defects in the MVZ tend to be deeper, and probably 
more numerous as well. See references 11 and 12 for a discussion of possible reasons for 
greater vulnerability of the MVZ.

In addition to local RNFL defects, many of the eyes with abnormal macular VFs and 
RGC+ maps showed what could be considered widespread damage. This damage included 
the macular region and, in some cases, was relatively mild. To extend the model, we assume 
that shallow widespread thinning of the disc is equally likely to appear in the inferior and 
superior macular region of the disc. Larger portions of the disc and, in some cases the 
entire disc, can be involved.

With the added assumptions about the nature of glaucomatous damage at the disc, the 
model explains a number of findings in the literature. First, as mentioned above, it has been 
reported that macular VF defects are more common in the upper VF, as well as more 
severe/deeper, and closer to fixation, as compared to defects in the lower VF. 4,5,9,10,13,16,27 
According to the model, this is primarily due to the asymmetric wiring (Fig. 1) combined 
with the relatively more common and deeper RNFL defects in the MVZ compared to the 
equivalent location in the upper disc near the border of the temporal and superior 
quadrants. Second, the relative preponderance of upper versus lower VF defects will 
depend upon the test used, as well as the criteria for abnormality. With the 10-2 VF test and 
criteria favoring local and/or deep defects,9,10,16,27 the relative number of upper VF defects 
will increase, while with the 24-2 VF test13 and criteria favoring subtle defects,7,13 the 
difference between the number of upper versus lower VF defects will decrease.

Clinical implications

Although the point has been made before, it is worth repeating here: damage to the all-
important macular region can be missed or underestimated with a VF test, like the 24-2, 
with a 6° test grid.8-13 Even deep local defects of the upper macular VF can be completely 
missed with the 24-2 VF test.10 However, typically if damage is confined to the central 10°, 
it will appear as one or two abnormal central points on the 24-2 VFs,10 as in the case of P5 
(Fig. 9A). The 24-2 test pattern needs modification unless it is routinely used with a 10-2 
test, which is often not the case.
Second, the subtle local VF defects associated with lower VF/superior macula, and/or widespread macular damage, may be overlooked or dismissed as insignificant based upon 24-2 VFs, especially if only pattern deviation (PD) plots are examined. The 24-2 VFs for P17 in Figure 9B provide an example. The PSD (1.62 dB) was in the normal range. Thus, macular damage can be missed if TD plots are ignored.

Third, the clinician is often faced with VFs that do not appear as typical or classic patterns. In general, macular damage can present with a variety of patterns on the 24-2 and 10-2 VFs depending upon relative contributions of widespread and local defects, as well as the location of the local defects. The circumpapillary RNFL plot, if properly analyzed, can help the clinician understand VF patterns that appear unusual or ambiguous, as well as help identify macular damage.

Fourth, for identifying local damage to the macula, we find the presentation in Figure 3A particularly helpful, and a careful scrutiny of the disc scan essential. The scan and RNFL plot are presented with the center of the temporal region of the disc in the center of the display, instead of the usual TSNIT arrangement, which is centered on the nasal quadrant. This NSTIN plot has the advantage of placing the important macular region in the center, rather than splitting it in half. [Note: the center of the temporal quadrant does not correspond to the midline of the VF (see Fig. 3C).] In the NSTIN format of Figure 3A, the macula is represented by the region between the red and blue lines in the center of the scan. It is also important that the scan itself is large enough so that the clinician can scrutinize carefully the macular region, looking for local thinning and checking the veridicality of the segmentation of the RNFL as all segmentation algorithms make mistakes. Figure 10 illustrates these points. This patient had a 24-2 VF test with a MD (-1.50 dB), a PSD (1.16 dB) and a GHT all within normal limits. While there were a few abnormal points on the 10-2 test, the 10-2 MD (-1.70 dB) and PSD (1.39 dB), however, were within normal limits (Fig. 10A). The RNFL profile produced by the machine (Fig. 10B) was also unremarkable. However, the algorithm appears to miss a thinning as indicated by the white arrow in panel B, which is at a higher magnification than in the typical OCT report. Panel C shows an enlargement of this region with and without correction. After correcting the segmentation algorithm, the RNFL plot (panel D) shows a clear abnormal region (black arrow). In fact, this very local thinning is in the region associated with macular damage of
the upper VF. An examination of the RGC+ thinning and probability plots confirms RGC+
damage as indicated by the arrows in panel E. As further evidence that this damage is the
source of the problem seen on the 10-2, the 10-2 results can be combined with RGC+ maps
as previously suggested. In panel F, the abnormal points from the 10-2 pattern deviation
plot in panel A are superimposed on the RGC+ maps after adjusting for RGC displacement.
The agreement confirms a local defect in the macula.

Finally, this study provides evidence that subtle thinning of the temporal quadrant can
be missed on RNFL plots. For example, both P10 and P12 had clear RGC+ thinning in the
inferior macula (Fig. 6) and the macular damage was confirmed with independent
evidence, an inter-eye comparison of RNFL thickness in the case of P12 and an abnormal
mfVEP in the case of P10. However, RNFL thickness in the temporal quadrant was in the
normal range for both eyes. This is presumably due to the relatively thin RNFL in the
temporal quadrant combined with the variability among healthy control eyes in this region.
In any case, this argues for looking at RGC+ maps, in addition to RNFL plots, when
evaluating fdOCT scans for glaucomatous damage. We find the RGC+ probability plots most
useful when combined with 10-2 VF data in a single plot as previously described and
illustrated in Figure 10F.

Summary

Early glaucomatous damage to the macula is due to widespread and/or local
circumpapillary RNFL defects. The local macular damage is more common, more severe,
and closer to fixation in the upper VF/inferior retina than in the lower VF/superior retina.
A model of glaucomatous damage of the macula predicts the location of both the
widespread and local defects. OCT scans of the circumpapillary RNFL and the macular
RGC+ layer can aid in the identification of these defects and help in the interpretation of 24-
2 and 10-2 VF tests.

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manuscript; and Drs. J. Liebmann and C. Tello for referring patients for the study.


Table 1. Basic information about the 20 eyes with abnormal 10-2 visual fields and OCT macular RGC+ scans.

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POAG: primary open angle glaucoma; XFG: exfoliative glaucoma; PG: pigmentary glaucoma; GS: glaucoma suspect; JOAG: juvenile open angle glaucoma; HTG: high tension glaucoma; NTG: normal tension glaucoma.
Figure Captions

Figure 1. A model of glaucomatous damage of macula. Modified from Hood et al.\textsuperscript{12}

Figure 2. The fdOCT RGC+ data from a patient (P1). A. A single optical coherence tomography (OCT) B-scan along the horizontal meridian from a macular cube scan. The retinal ganglion cell plus inner plexiform (RGC+) layer is shown. B. The macular RGC+ thickness map for each eye from the segmented cube scan. A continuous probability map (lower panel) and a 8x8 grid probability plot (right panel) were derived by comparing local thickness to that of the healthy control group.

Figure 3. A. A circumpapillary circle scan from P1 with the retinal nerve fiber layer (RNFL) segmented (upper panel) and, in the lower panel, the RNFL thickness profile along with the confidence regions for 5\% (yellow) and 1\% (red). B. A schematic of the optic disc showing the orientation and location of the circle scan. C. The schematic model (left) with the regions associated with each hemifield within the central ±8 along with (right) the schematic of the disc showing the regions the model associates with the superior retina (red) and inferior retina (blue).

Figure 4. Averaged data for eyes with abnormal 10-2 VF and fdOCT RGC+ only in the upper VF/inferior retina (A), only in the lower VF/superior retina (B) or in both upper and lower VFs retina (C). Each panel contains the average 10-2 total deviation plot (morphed and in pseudo-color), the RGC+ thickness map, and the circumpapillary RNFL thickness plot.

Figure 5. Upper Group (P1-7). Individual results for 7 patients whose OCT RGC+ maps and 10-2 visual field (VF) tests showed abnormalities in the inferior retina/upper VF. For each eye, the upper row shows the probability plot (left) and total deviation (TD) values for the 10-2 VF. The second contains the RGC+ thickness (left) and probability (right) maps. The color code for these plots is shown at the bottom of the figure. The bottom row is the circumpapillary RNFL thickness (black) with vertical lines indicating the region of the scan associated with the macula according to the model in Fig. 2. The color regions indicate the
confidence limits from machine controls (green: within 95%; yellow: between 95 and 99%; red: beyond 99%). All eyes are presented as right eyes; OCT data are in retinal view and VF data in field view. The blue rectangle shows the region of interest.

**Figure 6.** Upper Group (P8-13). Same as in Fig. 5 except for 6 patients whose OCT RGC+ maps and 10-2 visual field (VF) tests showed abnormalities in the superior retina/lower VF. The red rectangle shows the region of interest.

**Figure 7.** Both Group (P14-20). Same as in Figs. 5 and 6 except for 7 patients whose OCT RGC+ maps and 10-2 visual field (VF) tests showed abnormalities in both hemifields.

**Figure 8.** A. Circumpapillary OCT scans for P2. The dashed white lines show the boundaries of the quadrants, the red and blue arrows the regions associated with the model in Fig. 2; the white and yellow arrows point to deep local thinning, and the yellow rectangle the region expanded in the left panel. B,C. Same as A for P4 and P9. D-F. Same as in A without expanded panel for P17, P19, and P13.

**Figure 9.** A. The TD probability plot of P5’s 24-2 VF. B. The TD and pattern deviation (PD) probability plots of P17’s 24-2 VF.

**Figure 10.** OCT and VF results from an eye of a glaucoma suspect. A. The TD and PD probability plots for the 24-2 and 10-2 VF tests. B. The RNFL thickness plot and circumpapillary scan as in Fig. 3. C. An expanded view of the region near the arrow in panel B with and without the segmentation corrected. D. Same as in panel B, but with the automated segmentation corrected. E. The RGC+ thickness and probability maps in retinal view. F. The RGC+ thickness and probability maps in field view with the abnormal points from the 10-2 PD plot in panel A superimposed. Pseudo-color calibration bars are shown at the bottom of Fig. 5.
More vulnerable (outside macula)

Less vulnerable (inside macula)

More vulnerable (inside macula)

More vulnerable (outside macula)

Relatively preserved macular region. RGCs project to temporal quadrant.

More vulnerable macular region. RGCs project to inferior quadrant.

±8° radius
A. Fig. 2

B. Retinal View

Macula RGC+

Probability Map (8X8 grid)

Legend

- = 1% probability

- = 2% probability

- = 5% probability

Probability Map

- = 1% probability

- = 2% probability

- = 5% probability
Fig. 3

A. 

B. 

C.
A. Upper VF Abnormal (n=7)

Field View

Retinal View

B. Lower VF Abnormal (n=6)

Field View

Retinal View

C. Both Upper and Lower VF Abnormal (n=7)

Field View

Retinal View

-6         -4           -2          0
40        60         80        100

dB

um
Fig. 5

10-2 Field View

Retinal View

P1

P2

P3

P4

10-2 Field View

Retinal View
Fig. 5 (continued)
Fig. 6

10-2 Field View

Retinal View

Retinal View

P8

P9

P10

P11
Fig. 6 (continued)

10-2 Field View

Retinal View

P12

P13
Fig. 7 (continued)
Fig. 8

A. P2

B. P4

C. P9

D. P17

E. P18

F. P13
Fig. 9

A. P5  24-2 TD
B. P17  24-2 TD  24-2 PSD
Fig. 10

A. TD 24-2 PD

B. macula ±8°

C. Field View

D. Retinal View

E. Field View

F. Retinal View