CLINICAL SCIENCE

Correlating Structure With Function in End-Stage Glaucoma

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BACKGROUND AND OBJECTIVE: To correlate structure and function in eyes with end-stage glaucoma.

PATIENTS AND METHODS: Fifty-six eyes of 48 patients with glaucoma presenting with end-stage glaucoma underwent scanning laser polarimetry (SLP) imaging using a commercially available GDx-variable corneal compensator unit (GDx-VCC; Laser Diagnostics Technologies, Inc., San Diego, CA). End-stage glaucoma was defined by both disc appearance and standard automated perimetry visual field criteria. Standard automated perimetry parameters included: mean deviation, pattern standard deviation, and total deviation plot. GDx parameters included: TSNIT average, superior average, inferior average, TSNIT standard deviation, and nerve fiber indicator.

RESULTS: The visual field mean deviation was -26.75 ± 3.50 dB. The remaining retinal nerve fiber layer measured in this group of eyes was: TSNIT average, 29.76 ± 5.81 µm; superior average, 30.76 ± 6.25 µm; and inferior average, 31.14 ± 7.20 µm. A low structure–function correlation was found when analyzing separately the superior and inferior hemifields (R^2 = 0.00001, R^2 = 0.0016, respectively).

CONCLUSIONS: In eyes with end-stage glaucoma, very thin but existing retinal nerve fiber layer is found on SLP. Such values rarely dropped below 10 to 20 µm. A flattening of the GDx TSNIT pattern was seen, and the correlation between structure and function was not evident.

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INTRODUCTION

Much is known about the correlation of structure and function in early glaucoma.[1-5] The structural changes that precede any noticeable functional changes, as detected by standard automated perimetry, have resulted in the term "pre-perimetric glaucoma."[6-8] Numerous studies have correlated early structural changes in disc topography[9,10] and the retinal nerve fiber layer (RNFL),[11,12] changes that clearly precede any detectable standard automated perimetry visual field changes.[13] More sophisticated visual field tests were devised in an attempt to identify functional changes earlier in the course of the disease.[2]

In contrast to early glaucoma, little is known about the correlation between structure and function in end-

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stage disease. This correlation has direct bearing on the approach chosen for observing and treating patients known to have end-stage glaucomatous optic neuropathy.

Recent advances in imaging technology now allow more accurate quantification of the structural damage caused by glaucoma. The GDx-variable corneal compensator (GDx-VCC; Laser Diagnostic Technologies, Inc., San Diego, CA), a scanning laser polarimeter, is one such imaging device. It enables measurement of the peripapillary RNFL thickness by combining a confocal scanning laser ophthalmoscope with an integrated polarimeter. Polarized light undergoes a phase shift as it passes through polarizing media, such as the cornea, the crystalline lens, and the RNFL. This phase shift was previously shown to correlate with the thickness of the RNFL[14] and appears to be highly reproducible.[15-18]

In this study, patients diagnosed as having end-stage disease, based on combined visual field and optic disc criteria, were scanned using the GDx-VCC, a scanning laser polarimetry device with a variable cornea compensator, to compare the structure–function correlation in end-stage glaucomatous optic neuropathy.

PATIENTS AND METHODS

Patients

Fifty-six end-stage glaucomatous eyes of 48 patients were included in this study. Inclusion criteria were: no history of ocular disease apart from glaucoma, mild cataract, or both (no more than 2+ nuclear sclerosis or 1+ cortical or posterior subcapsular opacity), no history of ocular surgery in the past 3 months, and a standard automated perimetry visual field test performed within 3 months of the GDx-VCC scan. Exclusion criteria were: diabetic retinopathy, any neurological causes for visual field loss, non-glaucomatous optic atrophy, prior retinal surgery, or any other non-glaucomatous causes that might have affected the visual field or the status of the RNFL.

Patients were recruited at Hadassah Medical Center, Jerusalem, Israel, and L. V. Prasad Eye Institute, Hyderabad, India. Prior to commencing the study, each subject underwent a full eye examination by a glaucoma specialist, including a slit-lamp evaluation, gonioscopy, intraocular pressure measurement, dilated stereoscopic disc examination, and fundus indirect ophthalmoscopy. Informed consent was obtained from all participants, and an Institutional Ethics Committee approval was obtained.

Definition of End-Stage Glaucoma

For the purpose of this study, end-stage glaucoma was defined as a combination of both an optic disc that appeared to have end-stage glaucoma (defined as a vertical cup-to-disc ratio of 0.9 or greater and marked rim thinning and excavation) and an end-stage visual field, defined as a mean deviation worse than -20 dB, and only a central or temporal island remaining in the visual field grayscale (Figure). A previous publication has identified characteristics common to advanced visual field loss and analyzed why the mean deviation and the grayscale are the only Humphrey field analyzer parameters that accurately identify this subset of eyes.[19]

A visual acuity exclusion criterion of best-corrected distance acuity of 20/100 or less was introduced into this study for the sole purpose of excluding eyes in which a reliable GDx examination could not be performed due to the loss of central fixation. Although we were interested in keeping eyes with end-stage glaucoma and only a temporal (or other peripheral) remaining island of vision, a reliable GDx examination is unable to be performed in eyes lacking at least some central vision due to lack of fixation ability.

GDx-VCC Imaging

Each patient was scanned using a GDx-VCC, software version 5.1.0. The patient was instructed to fixate on the internal flickering fixation target. The operator was instructed to achieve a high-quality scan, as judged by his subjective impression, as well as a machine-produced quality score of at least 8 of 10. Patients unable to fixate steadily enough to be scanned were excluded.

From the 16 parameters appearing on the GDx printout, we chose the 5 parameters appearing on the first printout page, which are those chosen by the manufacturer to be the most informative and that are best able to discriminate between normal and glaucomatous eyes. Temporal, superior, nasal, inferior, temporal (TSNIT) average is the average RNFL thickness along a concentric machine-determined ring with an inner diameter of 2.4 mm and an outer diameter of 3.2 mm, centered on the optic disc. Superior average is the average of the RNFL thickness values of the points within the ring along the superior 120° section. Inferior average is the average of the RNFL thickness values of the points within the ring along the inferior 120° section. TSNIT standard deviation is the standard deviation of the data points within the measured ring. Nerve fiber indicator (NFI) is a sup-

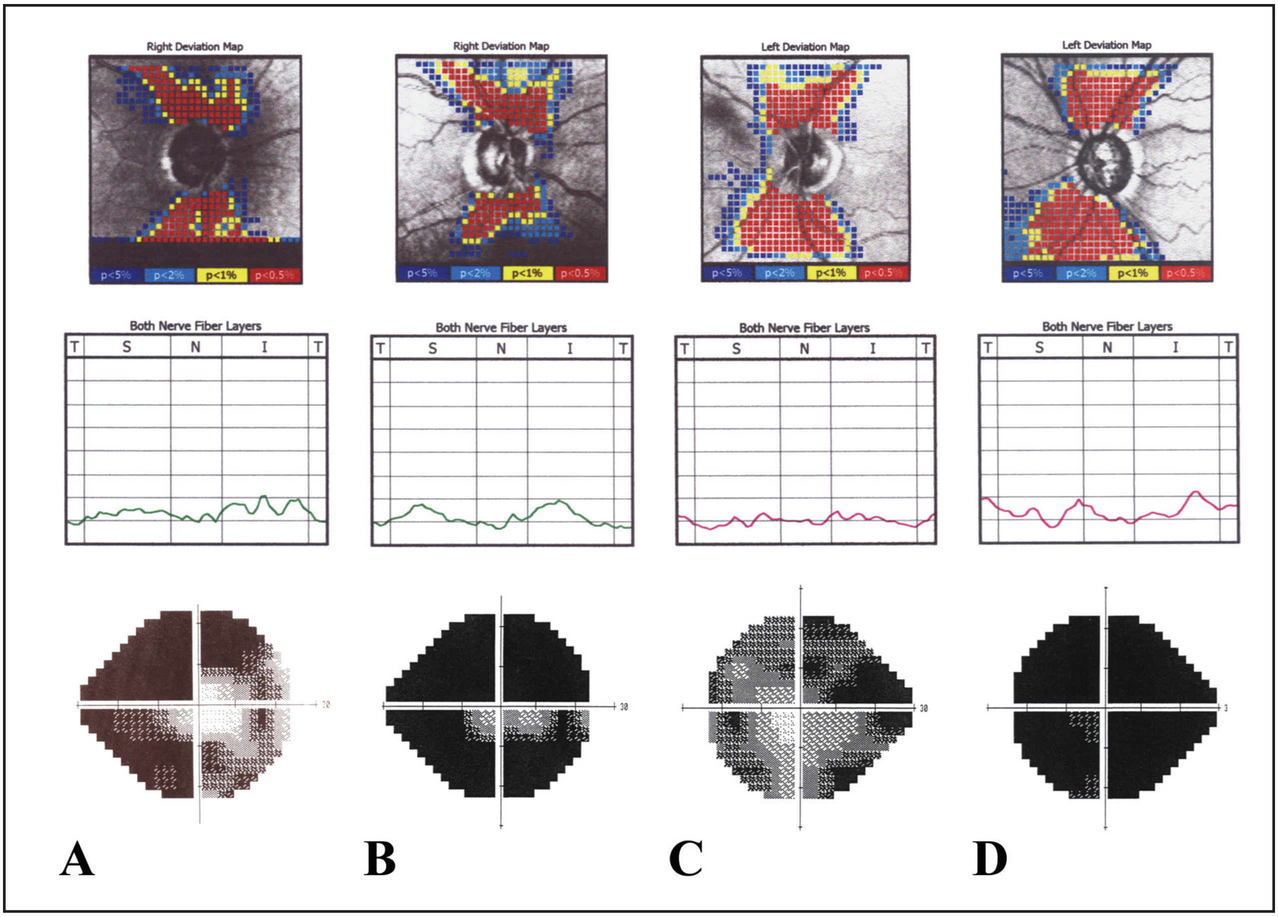

Figure. Four examples (A through D), from representative eyes with end-stage glaucoma included in this study, showing the GDx-variable corneal compensator (GDx-VCC; Laser Diagnostic Technologies, Inc., San Diego, CA) probability plots (upper row), temporal, superior, nasal, inferior, temporal average (TSNIT) retinal nerve fiber layer graphs (middle row), and visual field grayscale plots (lower row).

port vector machine-derived parameter indicating the likelihood that the eye is glaucomatous.

Visual Field Data

Standard automated perimetry visual fields were performed using the full-threshold, or SITA-standard, white-on-white 24-2 strategy. Mean deviation, pattern standard deviation, and total deviation plot were the statistical indices, and fixation losses, false-negative errors, and false-positive errors were the reliability indices used for analysis. A previous publication highlighted the limitations of Humphrey field analyzer statistical indices in advanced glaucomatous visual field loss.[19]

Structure–Function Hemifield Correlation

A structure–function comparison between the superior and inferior hemifields was performed as follows. From the GDx printout, we compared the superior average parameter value to the inferior average parameter value to determine the healthier (less damaged) hemifield. Next, we determined on the visual field printout which hemifield appeared healthier, based on averaging the raw threshold (dB) values in each of the hemifields.

Statistical Analysis

Paired *t* test, Pearson correlation, and analysis of variance were used for statistical analysis. Alpha error was set at less than 0.05. Data were analyzed using JMP statistical software version 5.0 (SAS Institute, Cary, NC).

RESULTS

Of the 48 patients included in this study, 40 were men and 8 were women. The mean age was 57.9 ± 14.08 years (range: 20 to 81 years). Twenty-nine right eyes and 27 left eyes were studied. The table lists func-

TABLE

Functional (VF) and Structural (GDx-VCC) Parameter Distribution

Parameter	Mean ± SD	Range
Mean deviation (dB)	-26.75 ± 3.50	-20.02 to -32.45
Pattern standard deviation (dB)	8.46 ± 2.79	1.89 to 17.06
NFI	94.05 ± 7.54	67.00 to 98.00
TSNIT (µm)	29.76 ± 5.81	19.42 to 43.75
TSNIT SD (µm)	6.77 ± 2.46	1.64 to 15.15
Superior average (µm)	30.76 ± 6.25	19.55 to 47.08
Inferior average (µm)	31.14 ± 7.20	19.74 to 46.46

VF = visual field; SD = standard deviation; NFI = nerve fiber indicator; TSNIT = temporal, superior, nasal, inferior, temporal.
The GDx-VCC is manufactured by Laser Diagnostic Technologies, Inc., San Diego, CA.

tional (visual field) and structural (GDx) parameter distribution.

As a group, eyes with end-stage glaucomatous optic neuropathy, as determined by combined structural (disc appearance) and functional (standard automated perimetry) criteria, showed a very thin, yet measurable, RNFL. The average overall RNFL thickness along a standardized 2.4 to 3.2 mm diameter ring (the TSNIT average parameter) in these eyes was 29.76 ± 5.81 µm (range: 19.42 to 43.75 µm). The pattern of RNFL loss in these eyes showed a flattening of the superior and inferior humps, such that the TSNIT graph showed a near even distribution (Figure), and hence the low TSNIT standard deviation values. As opposed to the massive loss superiorly and inferiorly, little RNFL loss was found in the nasal and temporal sectors.

Next, we identified the lowest measured RNFL thickness in any of these eyes. The lowest value obtained by the superior average parameter was 19.55 µm, whereas inferior average reached a minimum of 19.74 µm. In contrast to these averaged values (averaging a sector), judging from the actual TSNIT graph data, the lowest values seen in any of the eyes in any of the sectors reached a minimum of 10 µm, and never below that.

A comparison between the healthier hemifield as determined by structure and the healthier hemifield as determined by function revealed that for only 47.3% of the eyes did structure and function agree on which was the healthier hemifield, a value roughly what would be expected by chance alone. When we analyzed the actual numeric values (superior and inferior average [µm] for the GDx and superior vs inferior hemifield threshold values [dB] averaged for the visual field), a poor correlation between the upper and lower visual field hemifields was found (R^2 = 0.00001 and R^2 = 0.0016, respectively).

The highest RNFL peak for each of the eyes, as determined from the data along the TSNIT graph, was an averaged value of 43.1 ± 10.7 µm (range: 22 to 70 µm). We next set out to determine whether the highest TSNIT graph peak, indicative of the thickest RNFL bundle in each eye, was in agreement with the remaining visual field island, in terms of a superior versus inferior hemifield comparison. For only 50.9% of the eyes was an agreement found.

A low–moderate correlation was found between mean deviation and the following GDx parameters in these eyes with end-stage glaucoma: TSNIT average, superior average, inferior average, TSNIT standard deviation, and NFI (R^2 = 0.1, 0.1, 0.05, 0.05, and 0.02, respectively; pairwise correlations). No significant correlation was found between any of the GDx parameters and the following Humphrey field analyzer parameters: pattern standard deviation and the reliability indices.

After categorizing the eyes into two groups based on a mean deviation value of between -20 and -30 dB (n = 43) versus -30 dB and worse (n = 13), there was a statistically significant difference between the groups for the TSNIT average value, as measured by the GDx (P = .008, t test).

DISCUSSION

End-stage glaucoma in this study was defined using a combination of both structural and functional parameters. In early glaucoma, Kwon et al.[11] described a bilinear relationship between visual field parameters and RNFL thickness, such that visual field defects appear only when the RNFL thickness falls below a certain value, consistent with the assumption that structural damage precedes measurable functional deterioration. Furthermore, in their study, of all of the GDx parameters, the number had the highest correlation with the visual field mean deviation. Lan et al.[12] found that several GDx parameters (the number, maximum modulation, and ellipse modulation) showed high correlation with visual field indices, whereas no correlation was found between GDx parameters and the visual field pattern standard deviation parameter.

We are not aware of any published study that has examined structure–function correlation in end-stage glaucoma. It is not rare in glaucoma practice to encounter patients who retain good central acuity in the face of near-total RNFL loss, patients who are defined as legally blind.[20] At this time, as far as imaging state-of-the-art and clinical evaluation of the disc and RNFL, it appears that structure is less informative for such end-stage eyes and further follow-up might better rely on functional measures.

This is highlighted in the figure. Although the extent of visual field damage, as seen in the grayscale plots, seems to differ between these four eyes, the TSNIT graphs appear relatively uniform and are not able to differentiate between the severity of visual field defect found among these four eyes. Reus and Lemij studied the correlation between standard automated perimetry and the GDx-VCC and concluded that "patients with mild to moderate visual field loss in glaucoma may be better monitored with the GDx-VCC and patients who have severe loss, with standard automated perimetry" (p. 840), a conclusion that appears in line with our findings.[21]

The fact that RNFL thickness as determined with the GDx-VCC did not dip below 10 μm, even in eyes known to have little remaining vision (eyes in which the entire visual field grayscale appears black short of a small seeing island), suggests one of two possibilities. A measurement offset might exist in the data (also referred to as a floor effect); alternatively, the remaining RNFL supportive tissue present after most axons have been lost[22] might still possess birefringence properties.

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