Detection of Glaucoma With Scanning Laser Polarimetry

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Objective: To determine which retinal nerve fiber layer (RNFL) measures obtained with scanning laser polarimetry are most useful in detecting early to moderate glaucomatous visual field loss.

Subjects and Methods: One eye from 84 healthy individuals and 83 patients with early to moderate glaucomatous visual field loss (167 eyes) was assessed with a scanning laser polarimeter (Laser Diagnostic Technologies, San Diego, Calif). Three separate scans were obtained, and a baseline scan was created and used in the analyses. Integrated software (program GDx, version 1.0.02; Laser Diagnostic Technologies) was evaluated by assessing its sensitivity and specificity for detecting early and moderate glaucomatous visual field loss. Fisher linear discriminant functions also were developed in this population to assess sensitivity and specificity and were compared with the GDx analyses.

Results: There were statistically significant differences between the healthy and glaucomatous eyes for 14 of the 15 RNFL measures (P = .001). However, considerable overlap in measurements between groups was found. With the GDx number, the area under the receiver operator characteristic (ROC) curve was 0.78, and the sensitivity and specificity were 82% and 62%, respectively. Applying the best discriminant function using 3 variables (average thickness, ellipse modulation, and average ellipse thickness) to our study population resulted in an area under the ROC curve of 0.89 and a sensitivity and specificity of 74% and 92%, respectively.

Conclusions: A combination of RNFL measures obtained using the scanning laser polarimeter improved the ability to differentiate between healthy eyes and eyes with early and moderate glaucomatous visual field loss. Analyses using GDx software did not differentiate between healthy and glaucomatous eyes as well as the discriminant analysis function did.


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SUBJECTS AND METHODS

One eye from 84 healthy subjects and 83 patients with early to moderate glaucomatous visual field loss (167 eyes) was included. Forty-nine patients with glaucoma had early visual field loss, and 34 had moderate visual field loss. Intraocular pressure (IOP) or the appearance of the optic nerve head was assessed through a dilated pupil using biomicroscopy, applanation tonometry, gonioscopy, and dilated indirect ophthalmoscopy. The optic nerve head was assessed through a dilated pupil using biomicroscopy with a 78-diopter (D) lens. For inclusion in the study, scanning laser polarimetry and visual field testing were completed within 6 months of each other; mean ± SD time between testing was 0.7 ± 1.4 months.

All subjects underwent an ophthalmologic examination, automated visual field testing, stereoscopic photography, and scanning laser polarimetry of the peripapillary RNFL. The ophthalmologic examination included slit-lamp biomicroscopy, applanation tonometry, gonioscopy, and dilated indirect ophthalmoscopy. The optic nerve head was assessed through a dilated pupil using biomicroscopy with a 78-diopter (D) lens. For inclusion in the study, scanning laser polarimetry and visual field testing were completed within 6 months of each other; mean ± SD time between testing was 0.7 ± 1.4 months.

Visual field testing was performed using Humphrey Field Analyzer program 24-2 or 30-2 (Humphrey Systems, Dublin, Calif). Only the 24-2 points were used in the analysis to avoid rim artifacts. A pupil diameter of at least 3.0 mm was required for visual field testing, and only visual fields with reliability indices (fixation losses, false-negative rate, and false-negative rate) of no more than 25% were used. One randomly chosen eye per subject was included in the study.

HEALTHY SUBJECTS

Healthy subjects had no history of ophthalmologic or neurologic disease or surgery, no history of diabetes or other systemic diseases, and no use of medications known to affect visual field sensitivity. A family history of glaucoma was not an exclusion criterion. These subjects had normal results of an eye examination and a normal visual field with automated threshold perimetry. They had a best corrected visual acuity of 20/30 or better; spherical correction within ±5.0 D; cylinder correction within ±2.5 D; IOP of less than 22 mm Hg; and no history of elevation, open angles, or symmetric pattern standard deviation (CPSD) outside normal limits. Healthy subjects were recruited from volunteers in the community, hospital staff, and spouses or friends of patients.

PATIENTS WITH GLAUCOMA

Visual fields of 186 patients with glaucoma enrolled in a longitudinal study evaluating quantitative techniques for diagnosing and monitoring glaucoma were reviewed. Of these, 92 had repeatable early or moderate visual field loss and met each of the following criteria: GHT results outside normal limits or a CPSD outside 95% normal limits; and repeatable cluster of 3 or more points depressed at the 5% level on the pattern deviation plot on at least 2 visual fields (2 with achromatic automated perimetry or 1 with achromatic and short-wavelength perimetry). Short-wavelength fields were analyzed relative to our normative database of 99 eyes using a statistical analysis package for GHT and pattern deviation. Early visual field loss was defined by an MD of no worse than −6 dB (with at least 50% of test locations within normal limits) and a CPSD no worse than the 1% probability level. Moderate visual field loss was defined by an MD of no worse than −15 dB and a CPSD worse than the 1% probability level.

SCANNING LASER POLARIMETER

The scanning laser polarimeter (Nerve Fiber Analyzer [NFA]–GDx or NFA II; Laser Diagnostic Technologies, San Diego, Calif) is a confocal scanning laser ophthalmoscope with an integrated polarization modulator. Details of its operation have been reported previously.3,11 In brief, the light source, a polarization-modulated laser beam (wavelength, 780 nm), is directed to 1 point of the retina by the optical media of the eye, and the reflected light that double-passes the RNFL is detected to obtain the retardation at that point. The laser beam is directed sequentially over each of 256 × 256 retinal locations to obtain a retardation map in which each retinal location (pixel) has a corresponding retardation value. We used a field of view of approximately 15°. The acquisition time for these 65 536 data sets was 0.7 seconds. Other than the availability of a screening mode (which we did not use) and a normative database with the NFA-GDx, there are no differences between it and the NFA II.

Three retardation maps of the peripapillary retina of each eye were acquired, and a baseline map was automatically created and used for analysis by averaging the 3 retardation values corresponding to each pixel. The disc margin was established by an experienced operator who used a circle or ellipse to outline the inner margin of the peripapillary scleral ring.

Of the 92 eligible glaucomatous eyes, 9 were excluded due to spurious high reflectivity from zones of peripapillary atrophy (n = 6) or an insufficient number of available pixels for analysis (n = 3). None of the eligible healthy eyes were excluded. A total of 83 glaucomatous and 84 healthy eyes were included in the study. Measurement of 67 glaucomatous and 29 healthy eyes were obtained using the NFA II. The remaining 16 glaucomatous and 35 healthy eyes were acquired and analyzed using the NFA-GDx. All measurements were analyzed using NFA-GDx software. There were no significant differences between the mean values obtained with the NFA II and the NFA-GDx for each of the 15 RNFL measures in healthy eyes (for GDx number, P = .13; superior ratio, P = .83; inferior ratio, P = .80; superior/nasal ratio, P = .52; maximum modulation, P = .73; superior maximum, P = .96; inferior maximum, P = .49; average thickness, P = .37; volume, P = .43; ellipse modulation, P = .16; ellipse average, P = .83; superior average, P = .55; inferior average, P = .91; superior integral, P = .05).

Program GDx analyzes subsets of the 65 536 pixels in each of 4 quadrants (superior, inferior, temporal, and nasal). The GDx software uses a race- and age-specific normative database of more than 1100 eyes to classify 15...
measures of RNFL thickness as within normal limits, border-
line, or outside normal limits. According to the manu-
ufacturer, healthy patients aged 18 to 80 years were
enrolled at 6 sites using a standard protocol for inclusion
in the normative database. Healthy eyes could not have a
significant visual field defect, unreliable field, pathologic
appearance of the optic disc, or asymmetry of the cup-
disc ratio of more than 0.2. All patients had best-corrected
visual acuity of 20/40 or better and refractive error of
less than 5 D of sphere and less than 2 D of cylinder.
Patients were excluded if they reported a family history
of glaucoma or a history of elevated IOP (>21 mm Hg),
retinal disease, retinal surgery, or refractive surgery.
With GDx software, outside normal limits is defined as
outside 95% confidence limits. Borderline is defined as
outside 90% confidence limits. The healthy subjects
recruited for this study were not included in the GDx
normative database.

RNFL MEASURES

Fifteen RNFL measures per patient were automatically cal-
culated using GDx software. For GDx number, a trained
neural network assesses all pixels and assigns to an eye a
number from 0 to 100 (0 indicates normal; 100, advanced
glaucoma). A back-propagation type network with 2 hid-
den layers is used. The input layer consists of 128 input
neurons (number of parameters), and the output layer con-
sists of 1 output neuron (the diagnosis).

A total of 1500 pixels per quadrant peripheral to an
ellipse 1.75 disc diameters from the center of the disc was
used to calculate ratio and maximum measures. Symme-
try was the ratio of the average 1500 thickest pixels in the
superior quadrant divided by the average of the 1500 thick-
est pixels in the inferior quadrant. Superior ratio was the
ratio of the average of the 1500 thickest pixels in the su-
perior quadrant divided by the average of the 1500 me-
dian pixels in the temporal quadrant. Inferior ratio was the
ratio of the average of the 1500 thickest pixels in the infe-
rrior quadrant divided by the average of the 1500 median
pixels in the temporal quadrant. Superior-nasal ratio was
the average of the 1500 thickest pixels in the superior quad-
trant divided by the average of the 1500 median pixels in
the nasal quadrant.

For maximum modulation, first, the average is calcu-
lated for the 1500 thickest points in the superior and in-
ferior quadrants. Next, the 1500 median points in the na-
sal and temporal quadrants are calculated. The lowest of
these 4 values is subtracted from the highest, and then di-
vided by the lowest value.

Superior maximum was the average of the 1500 thick-
est pixels in the superior quadrant; inferior maxi-
mum, the average of the 1500 thickest pixels in the infe-
rrior quadrant; and average thickness, the average of all
pixels outside the disc margin that have a valid reading.
Pixel measurements obtained during an eye movement
were invalid and excluded from the calculation of average
thickness.

Volume was the average thickness multiplied by the
number of pixels × 0.000295 mm² (area of a pixel).

Ellipse modulation, ellipse average, superior aver-
age, and inferior average were calculated using pixels
within the 10-pixel-wide elliptical band that is automatically
positioned concentric with the disc margin outline and 1.75
disc diameters from the center of the optic disc. Ellipse
modulation was calculated by taking the thickest pixel
within the elliptical band, subtracting the thinnest pixel
within the band, and dividing the total by the value of the
thinnest pixel. Ellipse average was calculated using aver-
age thickness of the pixels within the elliptical band sur-
rrounding the optic nerve. Superior average was the aver-
age thickness of the pixels within the elliptical band in the
superior quadrant. Inferior average was the average thick-
ness of the pixels within the elliptical band in the inferior
quadrant. Superior integral was the total area under the curve
and within the superior portion of the elliptical band sur-
rrounding the optic nerve.

Optic disc area was measured using images obtained
with a confocal scanning laser ophthalmoscope (Heidel-
berg Retinal Tomograph, Heidelberg Engineering, Heidel-
berg, Germany). Corneal curvature was used to cor-
rect for magnification, and the disc margin was outlined
on the mean topography image.

STATISTICAL ANALYSIS

Analyses were completed using commercially available
software (JMP; SAS Institute, Cary, NC, and Splus, ver-
sion 3.4, MathSoft Inc, Seattle, Wash). Student t or χ² test
was used to evaluate differences between both study
groups. A P value of no more than .05 was considered sta-
tistically significant.

Fisher linear discriminant functions (LDFs) were
used to develop a classification rule. They were calcu-
lated to differentiate between groups, using all subsets of
the 15 RNFL measures and age. The ratio (between-group
variance to within-group variance) of each LDF was
examined to determine the relative importance of the dif-
f erent variables. The LDF is a score formed by taking a
weighted sum of the predictor variables and is chosen so
that the ratio is maximized. This ratio, which serves as a
criterion for assessing the usefulness of the LDF, was
examined to determine the relative importance of the dif-
f erent variables. Since all subsets of predictors were ex-
amined, we summarized the results by looking first at the
maximum ratio for subsets consisting of 1 variable, then
the maximum for subsets of 2 variables, and so on to see
whether the ratio would increase markedly if more vari-
ables were included.

A receiver operator characteristic (ROC) curve was
used to assess the ability to differentiate between healthy
and glaucomatous eyes. The ROC curves and the areas
beneath them were computed using direct calculation.
Differences of these areas were tested using the method of
DeLong et al. An area under the ROC curve of 1.0 indi-
cated perfect discrimination. An area of 0.5 indicated no
discrimination. A k-fold cross-validation on 12 randomly
chosen training and test sets was used to estimate the bias
in the area under the ROC curves from using the same
study population to identify and test the discriminant
function.

For the discriminant functions presented, we deter-
mined several appropriate cutoff points for sensitivity and
specificity estimates using subjective evaluation of the ROC
curve and by summarizing the sensitivities and specifici-
ties using various cutoffs.
The age, sex, refractive status, and race of the healthy subjects are presented in Table 1. There was no statistically significant difference in sex or race among the study groups, but the healthy subjects were significantly younger than the patients with glaucoma. For this reason, age was included as a candidate variable in the linear discriminant analyses.

There were statistically significant differences (P < .001) between the healthy and glaucomatous groups for all 15 RNFL variables measured except symmetry (P = .08) (Table 2). Each measure had low sensitivity when compared with the internal normative database (Table 3). We therefore created an all-normal variable that was within normal limits if comparison of each of the 14 measures (excluding the GDx number) with the internal normative database was within normal limits. The GDx number was excluded because there was no normative database. The sensitivity of all-normal was 90% (75/83), but the specificity was 93% (217/234). If a cutoff of 15 or 23 was used, the sensitivities were 92% and 64%, respectively, whereas the specificities were 56% and 77%, respectively.

With our 84 healthy and 83 glaucomatous eyes, the best LDF discriminant function formula using 3 variables was as follows:

\[
LDF = -4.442655 - (0.156 \times \text{Average Thickness}) + (0.935 \times \text{Ellipse Modulation}) + (0.183 \times \text{Ellipse Average})
\]

This discriminant function had a bias-corrected ROC curve area of 0.887. With an arbitrarily selected cutoff of less than −0.289 as normal, the LDF correctly labeled 76 of 84 healthy eyes (specificity, 92%) and 61 of 83 eyes with early to moderate glaucomatous visual field loss (sensitivity, 74%) (Table 4). However, if a value of 0.501 was used to classify healthy, the sensitivity of the formula increased to 88% (73/83), and the specificity to identify healthy eyes decreased to 68% (57/84).

There were several subsets of 3 variables that were competitive with the above formula. The parameters included in the best 20 discriminant functions of 3 variables are presented in Figure 1. Ellipse modulation and ellipse average were included in more subsets than any other variable, at 13 and 12 models, respectively. Age was included in only 6 of the 20 best models.

The LDF identified in the eyes with early to moderate visual field loss was applied to the group of eyes with early loss. Using a cutoff of −0.265, the sensitivity (61%) was lower compared with the combined group with early and moderate glaucomatous visual field loss (74%), whereas the specificity remained the same (93%). In addition, we developed an LDF using the eyes with early visual field loss only. The variables of the best-of-3 model were identical to the model developed using eyes with early and moderate visual field loss.

To further investigate whether the difference in age between the healthy and glaucomatous eyes was influencing our results, we completed the analysis in 2 age groups: no older than 60 and older than 60 years. In the group no older than 60 years consisting of 19 glaucomatous and 56 healthy eyes, the area under the ROC curve for the best-of-3 LDF model was 0.894. In the group older than 60 years consisting of 64 glaucomatous and 28 healthy eyes, the area under the ROC curve for the best-of-3 LDF model was 0.873. The area under the ROC curve for the GDx number for persons no older than 60 years was 0.786, and 0.670 for those older than 60 years.

Optic disc area was not included in any of the best 30 linear discriminant functions of 3 variables. In addition, we stratified our study population based on disc area...
In our study, there were statistically significant differences in the mean values of RNFL measures between the healthy subjects and patients with glaucoma. As with other glaucoma diagnostic tests used in clinical practice, ie, IOP or ophthalmoscopic assessment of the cup-disc ratio, there was overlap between the healthy and glaucomatous groups in the range of values for all of the measures. This overlap may be related to wide variations in the RNFL among healthy individuals. Such overlap is important, because it limits the usefulness of a test for diagnosing glaucoma without other corroborating findings. Moreover, the use of this instrument, or any other diagnostic instrument, to detect glaucoma depends on the demographic characteristics of the patient population and the severity of the disease.

Although none of the RNFL measures individually identified even half of these patients with early and moderate glaucoma as outside normal limits, our results indicate that the ability to differentiate between healthy and glaucomatous eyes can be improved by using a combination of them in a discriminant analysis function. Using a combination of measures also has been shown to improve the ability to discriminate between healthy and glaucomatous eyes with analysis of stereoscopic photographs and topographic optic disc parameters obtained with a confocal scanning laser ophthalmoscope. Given that the discriminating ability between 2 parameters may be similar, it is probable that 2 or more models will provide similar discriminating power. Our analysis strategy assessed this possibility by evaluating all 560 combinations of 3 variables using the Fisher LDF. We found many competitive discriminators using the Fisher LDF. We found many competitive discriminators using the Fisher LDF. 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analyses in our study are considerably less than those observed by Tjon-Fo-Sang and Lemij10 in an earlier study. They found a sensitivity and specificity of 96% and 93%, respectively. Although it is important to replicate estimates of sensitivity and specificity of diagnostic techniques in other study populations, it is often the case that initial reports of high sensitivity and specificity, even in well-designed studies, are difficult to replicate in different study populations. Several explanations may account for the differences in our study and that by Tjon-Fo-Sang and Lemij.10

We used NFA II or NFA-GDx, not the original NFA used in the earlier study,10 to reduce interoperator and intraoperator variability. The instruments used in our study contain a polarization detector that allows detection of polarized and unpolarized light. By electronically adding the polarized and unpolarized light components, it was able to recognize the intensity setting chosen by the operator. This feature was included to reduce interoperator variability and to minimize the dependency on the intensity setting of the original instrument.12 With the modified instrument, the dynamic range of the polarization detector was increased by approximately 30%.

Table 4. Sensitivity and Specificity of the GDx Analyses and LDF

<table>
<thead>
<tr>
<th>Classification</th>
<th>Analysis</th>
<th>Area Under ROC Curve</th>
<th>Cutoff Used to Classify as Glaucoma</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDx</td>
<td>GDx No. (n = 167)</td>
<td>0.78</td>
<td>&gt;15</td>
<td>92</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>GDx No. (n = 167)</td>
<td>0.78</td>
<td>&gt;17</td>
<td>82</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>GDx No. (n = 167)</td>
<td>0.78</td>
<td>&gt;23</td>
<td>64</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>All within normal limits</td>
<td>NA</td>
<td>NA</td>
<td>86</td>
<td>57</td>
</tr>
<tr>
<td>LDF</td>
<td>Best of 3 variables (n = 167)</td>
<td>0.91</td>
<td>-0.289</td>
<td>74</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>Best of 3 variables (n = 167)</td>
<td>0.91</td>
<td>0.501</td>
<td>68</td>
<td>68</td>
</tr>
</tbody>
</table>

* GDx analyses were determined using GDx software (version 1.0.02; Laser Diagnostic Technologies, San Diego, Calif). LDF indicates Fisher linear discriminant function; ROC, receiver operator characteristics; and NA, not applicable.
This allowed a wider range of retardation value to be delineated. These values are displayed in a retardation map, and a fundus image also is displayed, allowing for better visibility of the optic disc.  

The discrepancies between these studies also may be related to differences in data analysis. All images in our study were analyzed using GDx software for analysis, and this was not available when the earlier study was conducted. The GDx software includes a relatively large age- and race-specific normative database to automatically classify measurements as outside normal limits. It also includes the GDx number, which was developed based on the results from a back propagation neural network that included healthy subjects and patients with glaucoma. Moreover, we assessed the mean retardation data from 3 measurements in each eye rather than just 1 measurement, as in the earlier study.

Perhaps the most important reason for the discrepancies in the results of these studies relates to the severity of glaucoma included in each of them. In the earlier study, patients were included in the glaucoma group if they had results of a GHT that were outside normal limits. The MD of the included patients was −10.33 dB (range, −31.5 to 0.76 dB). Therefore, they included patients with early defects and patients with severe visual field loss. In contrast, our study was designed to include patients only with early or moderate visual field loss. Each of them had repeatable early or moderate visual field loss and results of a GHT outside normal limits or a CPSD outside 95% normal limits, and a repeatable cluster of 3 or more points depressed at the 5% level on the pattern deviation plot on at least 2 visual fields. Patients were excluded if MD was worse than −15 dB.

In both studies, the healthy subjects were not a part of the normative data used to determine outside normal limits. As we compared only patients with early or moderate glaucoma with healthy subjects, and Tjon-Fo-Sang and Lemij compared patients with advanced glaucoma as well, it is not surprising that they found higher sensitivity and specificity.

One limitation of our study was that we did not test our discriminant function on another cohort of subjects to independently estimate its sensitivity and specificity. However, we provided estimates of the bias in the calculation of the area under the ROC curve by using a k-fold cross-validation on 12 randomly chosen training and test sets. The bias was relatively small, resulting in a reduction of the area under the ROC curve of approximately 1.8% in the best-of-3 LDF model. Roughly the same amount of bias is inherent in the sensitivity and specificity estimates as in the area under the ROC curve. Therefore, it is our best estimate that the sensitivity and specificity values presented using cutoffs of 0.289 and 0.501 are overstated by approximately 1.8%.

In conclusion, we showed that using a combination of RNFL measures obtained using the scanning laser polarimeter improved the ability to differentiate between healthy eyes and eyes with early and moderate glaucomatous visual field loss. The GDx number and normative database provided with the software did not differentiate between healthy and glaucomatous eyes as well as the LDF. Further study is needed to determine whether the automated analysis features of the normative data and neural network can improve the clinical usefulness of the instrument for detection of early and moderate glaucoma.

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