Slope of the Peripapillary Nerve Fiber Layer Surface in Glaucoma

Joseph Caprioli, Hyun Joon Park, Seyda Ugurlu, and Douglas Hoffman

PURPOSE. To develop structural markers of early glaucomatous optic nerve damage with confocal scanning laser ophthalmoscopy.

METHODS. Custom software was developed to analyze the images of 53 patients with open-angle glaucoma and 43 healthy subjects (matched for age, race, and refractive error), with images acquired with a confocal scanning laser ophthalmoscope. Height values were obtained along radial profiles of the peripapillary nerve fiber layer surface at 5-degree intervals around the disc edge. Two new parameters were derived: mean height and mean slope of the peripapillary nerve fiber layer surface. Mean slope was tested for its independence from a retinal reference plane. A logistic regression analysis was used to determine functions of disease probability. Receiver-operating characteristic (ROC) curves were used to evaluate sensitivity and specificity of peripapillary nerve fiber layer slope and height to discriminate normal subjects from glaucoma patients.

RESULTS. Mean (±SD) visual field mean deviation in the glaucoma group was −4.8 ± 3.3 dB. Mean slope (±SD) of the peripapillary nerve fiber layer was significantly (P < 0.001) steeper (0.30 ± 0.12) in glaucoma patients than in healthy subjects (0.11 ± 0.12). Mean slope values were identical with or without the retinal reference plane. Mean height (±SD) values with respect to a retinal reference plane were 45.2 ± 103 μm in healthy subjects and −65.2 ± 105 μm in glaucoma patients, which were significantly different (P < 0.001). The differences for mean slope and for mean height between the healthy subjects and the glaucoma patients were greatest inferiorly. The diagnostic precision, sensitivity, and specificity of mean slope were 83%, 85%, and 80%, respectively. The diagnostic precision, sensitivity, and specificity of mean height were 75%, 69%, and 83%, respectively.

CONCLUSIONS. Mean peripapillary slope of the nerve fiber layer surface can be used to discriminate between healthy subjects and glaucoma patients with clinically useful diagnostic precision. This parameter is independent of a retinal reference plane and may be particularly useful to detect progressive glaucoma damage. (Invest Ophthalmol Vis Sci. 1998;39:2321-2328)

Because technological advances have provided the ability to extract quantitative information from digitized images of the optic nerve head and peripapillary nerve fiber layer, efforts have been made to determine a reliable structural marker for early glaucomatous optic nerve damage. Confocal scanning laser ophthalmoscopy has been introduced recently, and its reproducibility and ability to provide early-phase results in glaucoma patients have been reported. It is not clear which of the many summary structural parameters possible with this technique, singly or in combination, are the most sensitive and specific diagnostic markers for early glaucoma damage. Uchida et al. recently reported that cup shape measure was the parameter that discriminated best between normal structure and early glaucoma. However, most of these structural parameters are derived from images obtained after the application of a retinal reference plane, and such planes are subject to change with time as glaucoma damage progresses.

In this study, we developed two new structural parameters, the slope and height of the peripapillary nerve fiber layer surface, and examined their ability to perform as a measure of early optic nerve damage due to glaucoma.

SUBJECTS AND METHODS

We analyzed images obtained with a confocal scanning laser ophthalmoscope (Heidelberg Retinal Tomograph [HRT]; Heidelberg Engineering GmbH, Heidelberg, Germany) from 53 patients with early primary or secondary open-angle glaucoma and 43 healthy subjects; this database of subjects is identical to that reported in a previous study. Healthy subjects were recruited from hospital staff and spouses or friends of patients and were matched with glaucoma patients for age, race, and refractive error. Visual field tests were performed with program G1 or G2 of the Octopus perimeter (Interzeag, Schlieren, Switzerland) or program 24-2 or 30-2 of the Humphrey Field

Copyright © Association for Research in Vision and Ophthalmology

2321
TABLE 1. Characteristics of the Study Group

<table>
<thead>
<tr>
<th>Race</th>
<th>Healthy Subjects (n = 43)</th>
<th>Glaucoma Patients (n = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>African-American</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Asian</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>37</td>
<td>47</td>
</tr>
</tbody>
</table>

Age (y)                      mean ± SD, 50.9 ± 13.6 56.1 ± 10.0
Refractive error (D)          mean ± SD, −0.3 ± 1.5 −0.6 ± 2.0
Mean deviation (decibels)*    mean ± SD, −0.4 ± 1.7 −4.8 ± 3.3
Corrected pattern standard deviation, decibels* mean ± SD, 1.1 ± 0.8 5.4 ± 3.8

Values are means ± SD. *P < 0.001.

TABLE 2. Mean Peripapillary Slope of the Nerve Fiber Layer Surface without a Retinal Reference Plane

<table>
<thead>
<tr>
<th>Slope</th>
<th>Healthy Subjects (n = 43)</th>
<th>Glaucoma Patients (n = 53)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal</td>
<td>0.32 ± 0.02 (0.32 ± 0.02)</td>
<td>0.47 ± 0.03 (0.47 ± 0.03)</td>
<td>0.005</td>
</tr>
<tr>
<td>Superior</td>
<td>0.14 ± 0.10 (0.14 ± 0.10)</td>
<td>0.31 ± 0.11 (0.31 ± 0.11)</td>
<td>0.000</td>
</tr>
<tr>
<td>Nasal</td>
<td>0.00 ± 0.04 (0.00 ± 0.04)</td>
<td>0.19 ± 0.05 (0.20 ± 0.05)</td>
<td>0.000</td>
</tr>
<tr>
<td>Inferior</td>
<td>0.07 ± 0.13 (0.07 ± 0.13)</td>
<td>0.30 ± 0.13 (0.30 ± 0.13)</td>
<td>0.000</td>
</tr>
<tr>
<td>Overall</td>
<td>0.11 ± 0.12 (0.11 ± 0.12)</td>
<td>0.30 ± 0.12 (0.30 ± 0.13)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Values are means ± SD. Values within the parentheses refer to slope data with the reference plane.

* With Bonferroni correction.
for calculating heights and slopes was repeated for 1- and 10-degree intervals, and the area under ROC curves, sensitivities, and specificities were calculated. Mean height and mean slope values from four sectors (temporal 80°, superior 70°, nasal 140°, and inferior 70°) were also calculated individually.

The average surface contour map (identified by the software as a "MOP" image) of three sequential individual images (identified by the software as a "TOP" image) taken of the same eye at the same sitting was used for these calculations, and the data are reported here. In a separate reproducibility study of the height and slope measurements, the standard deviations of 3 sets of repeated height and slope measurements were calculated in a separate group of 10 normal (healthy) and 10 glaucomatous eyes, who met the criteria specified above. The average of these standard deviations is reported for height and slope in the normal and glaucoma groups separately and is a measure of the reproducibility of the technique.

Mean slope and mean height values for the healthy and glaucoma groups were compared. A Bonferroni correction was applied when multiple, simultaneous t-tests were performed.

The mean slope and mean height of each subject were applied to a logistic regression model separately and in combination, to estimate a probability function for the presence of glaucoma. The model can be written as follows: probability (glaucoma) = 1/(1 + e^{-Z}), where Z is the linear combination of multiple (p) independent variables and Bp are their coefficients: Z = B0 + B1X1 + B2X2 + ... + BpXp, where X is either the mean slope or mean height.

All data were randomly divided into three subsets (A, B, and C). The proportion of healthy and glaucomatous eyes in each subset was constant. Two subsets (e.g., A and B) were used to calculate the probability functions. The probability function thus derived was applied to the remaining subset (in this example, C) to estimate the probability of glaucoma for each subject in the subset. Subsequently, to estimate the probabilities of subsets A and B, the functions were derived from B and C, and A and C, respectively. Sensitivities, specificities, and diagnostic precisions for mean slope and mean height were calculated, and the ability of these parameters to discriminate between healthy and glaucomatous eyes was investigated with ROC curves, which were plotted with the probabilities provided by the logistic regression analysis. The areas under the ROC curve were calculated. Statistical comparisons of the areas under the ROC curves were performed with nonparametric statistics. Diagnostic precision is the overall proportion of correct diagnostic assignments to the healthy and glaucomatous groups.

Octopus visual field indices (mean defect and corrected loss variance) were converted to Humphrey visual field index format, mean deviation (MD), and corrected pattern SD (CPSD), according to the method described by Zeyen et al. The correlations between visual field indices (MD and CPSD) and mean peripapillary slope and height were performed with Pearson product moment correlation.

RESULTS

In 53 open-angle glaucoma patients, there were 43 eyes with primary open-angle glaucoma, 7 with pigment dispersion syndrome, 2 with pseudoexfoliation syndrome, and 1 with secondary open-angle glaucoma. The eyes used for analysis were as follows: glaucoma, 24 right and 29 left; normal (healthy), 19 right and 24 left. Average visual field MD and CPSD were statistically different in the healthy and glaucoma groups (P < 0.001). There were no statistically significant differences for age, race, or refractive error. The characteristics of the study population are shown in Table 1.

The separate reproducibility study revealed the following. The average variability (expressed as the average SD of three
repeated measurements for all height values) was 19 μm in the healthy subjects and 21 μm in the glaucoma patients. The average variability (expressed as the average SD of three repeated measurements for slope values) was 0.045 for the normal subjects and 0.021 for the glaucoma patients. The latter values, expressed as a percentage of the range of slope measurements in normal subjects and glaucoma patients, were 2.1% and 2.2%, respectively.

Mean peripapillary slope values were the same with or without the retinal reference plane (Table 2, Fig. 1). Mean slopes (±SD) were 0.11 ± 0.12 in healthy subjects and 0.30 ± 0.12 in glaucoma patients (P < 0.001, Fig. 2). The mean slopes were significantly different between normal and glaucoma groups in the temporal, superior, nasal, and inferior sectors (P = 0.005, P < 0.001, P < 0.001, and P < 0.001, respectively). The inferior sector had the largest area under the ROC curve (Table 2, Fig. 3).

Height values without the retinal reference plane provided lower sensitivity (60%), lower specificity (63%), and a smaller area under the ROC curve (0.66) than height values computed with the retinal reference plane (Table 3, Fig. 1). The following are the results with the retinal reference plane. The mean height (±SD) values were 45 ± 103 μm in the normal group and −65 ± 105 μm in the glaucoma group (P < 0.001, Table 3, Fig. 2). Mean heights were significantly different between normal and glaucoma groups in the temporal, superior, nasal, and inferior sectors (P = 0.04, P < 0.001, P < 0.001, and P < 0.001, respectively). The inferior sector had the largest area under the ROC curve (Table 3, Fig. 3).

Table 4 shows the sensitivities, specificities, and diagnostic precisions for mean peripapillary slope and height. For mean slope without the reference plane, the diagnostic precision, sensitivity, and specificity were 83%, 85%, and 81%, respectively. For mean height with the reference plane...
Slope of Peripapillary Surface in Glaucoma

1.0 - B
1.0 - 0.0
0.0 - 0.0
0.0
-112 ± 39
100.4 ± 57.5
96 ± 42
615 ± 77.6
45 ± 103
(-112 ± 39)
(56 ± 56)
(-25 ± 42)
(-49 ± 77.1)
(-24 ± 624)

Inferior (0.82)
Nasal (0.79)
Superior (0.78)
Temporal (0.70)

0.2 0.4 0.6 1.0
Specificity

0.0 0.2 0.4 0.6 0.8 1.0
Sensitivity

1 - Specificity

Peripapillary Slope

Peripapillary Height

A

B

FIGURE 3. (A) Receiver-operating characteristic (ROC) curves of mean peripapillary slope in four sectors. (B) ROC curves of mean peripapillary height in four sectors.

plane, these values were 75%, 69%, and 83%, respectively. When mean slope and mean height were considered together as covariates, diagnostic precision, sensitivity, and specificity were 82%, 83%, and 80%, respectively. Figure 4 shows the ROC curves plotted for mean slope and mean height. The areas under the ROC curves were 0.86 for mean slope and 0.79 for mean height, which were not significantly different (P = 0.19).

The height and slope calculations were repeated for 1- and 10-degree intervals; the results obtained for the areas under the ROC curves, sensitivities, and specificities were very similar (and not statistically significantly different) to those obtained with 5-degree sampling intervals.

The mean peripapillary slope and mean peripapillary height in glaucoma patients were both significantly correlated with MD and CPSD (Table 5).

**DISCUSSION**

Structural changes of the optic nerve head and nerve fiber layer can be evaluated by qualitative and quantitative methods. Stereoscopic color photography of the optic disc is an important method to record and assess optic disc appearance and glaucoma progression. High contrast monochromatic photographs of the nerve fiber layer are being used qualitatively to detect early damage, before measurable visual field defects are manifest. Stereophotogrammetry, planimetry, computerized image analysis of digitized images, confocal scanning laser ophthalmoscopy, laser polarimetry, and optical coherence tomography are quantitative methods under evaluation for the structural assessment of the optic nerve head and the nerve fiber layer.

Confocal scanning laser ophthalmoscopy is a recently introduced method that is reasonably reproducible and capable of detecting glaucoma damage early. The average SD was 0.015 mm³ for optic disc cup volume measurements from 10 recordings of one eye of 8 normal subjects. Five independent topographic images of the optic nerve head of eight healthy eyes and eight eyes with primary open-angle glaucoma were obtained with a laser tomographic scanner. The standard deviation of a single height measurement in normal eyes was 38.7 μm (range, 23.4–62.2 μm) for areas in the peripapillary retina and 42.6 μm (range, 24.4–53.7 μm) for measurements within the optic nerve head area. In glaucomatous eyes, the standard deviation was 41.2 μm (range, 23.2–59.6 μm) in the peripapillary retina and 49.4 μm (range, 28.1–72.8 μm) within the optic nerve head. Another study of 30 images of right optic nerves of 19 normal eyes found the 95% confidence interval of 0.035

<table>
<thead>
<tr>
<th></th>
<th>Healthy Subjects (n = 43)</th>
<th>Glaucoma Patients (n = 53)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal</td>
<td>-112 ± 39</td>
<td>-203 ± 30</td>
<td>0.035</td>
</tr>
<tr>
<td>Superior</td>
<td>106.4 ± 57.5</td>
<td>-3.7 ± 65.5</td>
<td>0.000</td>
</tr>
<tr>
<td>Nasal</td>
<td>96 ± 42</td>
<td>-12 ± 36</td>
<td>0.000</td>
</tr>
<tr>
<td>Inferior</td>
<td>61.5 ± 77.6</td>
<td>-74.5 ± 66.2</td>
<td>0.000</td>
</tr>
<tr>
<td>Overall</td>
<td>45 ± 103</td>
<td>-65 ± 105</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Values are means ± SD in micrometers. Values within the parentheses refer to height values without a retinal reference plane.

*With Bonferroni correction.
TABLE 4. Sensitivity, Specificity, and Diagnostic Precision of Mean Peripapillary Slope and Height

<table>
<thead>
<tr>
<th></th>
<th>Mean Peripapillary Slope (%)(^*)</th>
<th>Mean Peripapillary Height (%)(\dagger)</th>
<th>Combined (%)(\ddagger)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>85</td>
<td>69</td>
<td>83</td>
</tr>
<tr>
<td>Specificity</td>
<td>81</td>
<td>83</td>
<td>80</td>
</tr>
<tr>
<td>Diagnostic precision</td>
<td>83</td>
<td>75</td>
<td>82</td>
</tr>
<tr>
<td>ROC area under the curve</td>
<td>0.86</td>
<td>0.79</td>
<td>0.85</td>
</tr>
</tbody>
</table>

ROC, receiver-operating characteristic.

* Without the retinal reference plane.

\(\dagger\) With the retinal reference plane.

\(\ddagger\) Mean slope without reference plane and mean height with reference plane combined.

The mean slope of the peripapillary nerve fiber layer surface that incorporated information collected outside the disc edge. With a 10-degree image, topographic data less than 250 μm from the disc edge are uniformly available. Height measurements along the radial profiles that start from the disc edge and terminate 250 μm from the disc edge were obtained to describe two new parameters: mean height and mean slope of the peripapillary nerve fiber layer surface. We used the terminology "peripapillary nerve fiber layer surface height" rather than "RNFL thickness" because the heights are derived relative to a reference plane. The retinal reference plane used here has been described previously. The areas used to construct the plane represent the thinnest areas of nerve fiber layer within the image margins and those that may change least with progressive glaucoma damage.

The mean slope of the peripapillary nerve fiber layer surface was, by definition, expected to be independent of a retinal reference plane. Calculation of this parameter with and without the retinal reference plane produced identical values. The peripapillary nerve fiber layer surface had a more level approach toward the optic nerve head in normal individuals rather than a declining approach toward the optic disc such as that seen in glaucoma patients (Fig. 5). The region from which slope measurements were obtained corresponded to the peripapillary area immediately adjacent to the optic nerve head. The difference in the inclination of the nerve fiber layer surface in this region is reasonably sensitive and specific for glaucoma damage. At first glance our findings may seem contrary to intuition. One may think that the slope away from the disc of the nerve fiber layer surface might become less steep with the loss of fibers. Figure 5 helps to illustrate our findings. Nerve fibers lost from the optic disc rim cause the nerve fiber layer

![Peripapillary Slope and Height](image)

**Figure 4.** Receiver-operating characteristic curves of the overall mean peripapillary slope and mean peripapillary height. The areas under the curve are shown in parentheses.

TABLE 5. Correlation of Visual Indices with the Mean Peripapillary Slope and Height in Glaucoma Patients

<table>
<thead>
<tr>
<th></th>
<th>Mean Peripapillary Slope*</th>
<th>Mean Peripapillary Height†</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD</td>
<td>-0.428</td>
<td>0.328</td>
</tr>
<tr>
<td>(r)</td>
<td>&lt;0.001</td>
<td>0.005</td>
</tr>
<tr>
<td>CPSD</td>
<td>0.43</td>
<td>-0.305</td>
</tr>
<tr>
<td>(p)</td>
<td>0.001</td>
<td>0.028</td>
</tr>
</tbody>
</table>

MD, mean deviation; CPSD, corrected pattern standard deviation.

\(n = 53\) glaucoma patients.

* Without the retinal reference plane.

† With the retinal reference plane.
FIGURE 5. Radial profiles from a glaucoma patient and a healthy subject. Note that near the disc edge, the nerve fiber layer slopes toward the disc, and its surface lies below the retinal reference plane in the patient with glaucoma. It has a more level approach near the disc edge, and its surface lies above the retinal reference plane in the healthy subject.

A surface proximal to the disc edge to actually decline in slope into the enlarged cup of the glaucomatous eye, as shown in Figure 5. Comparison of Figure 5 with the normal anatomy as illustrated very well by Varma and colleagues is consistent with this finding.

Acquired peripapillary atrophy of the choroid can contribute to a decrease of the measured surface height in glaucomatous eyes. Thus, nerve fiber layer thinning alone need not be responsible for all the differences in surface topography between the two groups. It is not possible to calculate or deduce to what degree acquired peripapillary atrophy has contributed to the measurement of slopes presented here. Peripapillary atrophy is known to progress with glaucomatous optic neuropathy, and the net effect on the slope could well be a combination of peripapillary atrophy and loss of nerve fiber layer.

The mean height (±SD) values were 45 ± 103 μm in healthy subjects and −65 ± 105 μm in glaucoma patients. The negative mean value in glaucoma patients indicates height measurements below the retinal reference plane, whereas healthy subjects had mean height measurements above the retinal reference plane. These results are in accordance with the expectation that healthy subjects have a thicker nerve fiber layer than glaucoma patients (Fig. 5). Height measurements obtained without the use of the retinal reference plane resulted in greater variability, lower sensitivity, and lower specificity; they were not considered for further analysis.

In the study of Uchida et al., in which the same patient database as ours was used, neither of the two parameters that refer to the "thickness" of the nerve fiber layer along the disc edge contour line proved to be helpful diagnostically. RNFL thickness and RNFL cross-sectional area provided areas of 0.69 and 0.62 under their ROC curves, respectively; and no statistically significant difference was found between normal individuals and glaucoma patients. The parameter mean height of the peripapillary nerve fiber layer surface had an area of 0.79 under the ROC curve and had mean values that were significantly lower in glaucoma patients than in healthy subjects. The largest differences for mean slope and mean height between the healthy subjects and the glaucoma patients were located inferiorly. This supported the results of a previous study in which significant thinning of the inferior nerve fiber layer in glaucomatous eyes was shown by optical coherence tomography.

Structural parameters derived from height values have the disadvantage of being dependent on retinal reference planes. Every retinal reference plane, including the one used in this study, bears the major drawback of being shifted downward with advancing glaucoma damage, which could diminish measured changes. Independence from a retinal reference plane is therefore desirable, especially for detection of changes over time. In this study, mean peripapillary surface height and slope provided good sensitivity, specificity, and diagnostic precision. However, mean peripapillary slope has the additional advantage of being independent of a retinal reference plane and is therefore a promising parameter for monitoring progressive glaucoma damage.

References


