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Discrimination between normal and glaucomatous eyes with scanning laser polarimetry and optic disc topography: A preliminary report

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PURPOSE. To test the ability of structural parameters (as measured by scanning laser polarimetry (SLP) software 1.0.12 and confocal scanning laser ophthalmoscopy (CSLO) to discriminate between normal and glaucomatous eyes.
METHODS. A total of 112 patients with primary open-angle glaucoma and 88 normal individuals were enrolled in the study. All individuals underwent a thorough ophthalmic evaluation, a 24-2 full threshold Humphrey visual field, SLP with the GDx, and CSLO with the TOPSS. Patients with marked cataract or low vision were excluded from the study. Cut-off points were selected and receiver operator characteristic (ROC) curves were created for each individual CSLO and SLP parameter. Finally, multivariate discriminant formulas were developed in order to achieve a better sensitivity (Se)/specificity (Sp) ratio for the diagnosis of glaucoma, initially separately for each device, and then combining parameters from CSLO and SLP.
RESULTS. The mean deviation for the glaucoma group was –10.63 ± 7.58 dB. Multivariate discriminant formulas resulted in better sensitivity/specificity ratios than any individual parameter, either for CSLO (Se: 90%; Sp: 81%; accuracy: 86%) or SLP (Se: 87%; Sp: 86%; accuracy: 86%). The multivariate formula combining parameters from both devices resulted in an improvement in the ability to diagnose glaucoma. An area under the ROC curve of 0.97 was obtained, with a sensitivity of 93%, a specificity of 91%, and an accuracy of 92%.
CONCLUSIONS. The combination of structural parameters derived from CSLO and SLP in a multivariate discriminant formula may enhance the ability to diagnose glaucoma. Further studies investigating a random population are needed in order to test the validity of this formula. (Eur J Ophthalmol 2005; 15: 353-9)

KEY WORDS. Confocal scanning system, Glaucoma, Multivariate analysis, Visual field

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INTRODUCTION

Glaucoma is a multifactorial disease characterized by irreversible damage to the retinal nerve fiber layer (RNFL) and optic disc. Clinical diagnosis is based on the association of a classic pattern of visual field loss and typical optic disc damage. However, clinical assessment of the optic disc and RNFL is subject to large inter - and intraobserver variabilities (1, 2). Although perimetric defects are still considered as the gold standard in the diagnosis of glaucoma, glauco-

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matous changes to the optic disc (3) and RNFL may precede the onset of visual field loss by 5 years or more (4-6).

New devices developed to objectively measure RNFL thickness and optic disc topography have recently become available, including the scanning laser polarimeter (SLP) (7, 8) and the confocal scanning laser ophthalmoscope (CSLO) (9-12). However, because the optic disc and nerve fiber layer characteristics are subject to significant variability (13, 14), it has been postulated that combining two or more optic disc or nerve fiber layer parameters may enhance the ability to discriminate between normal and glaucomatous eyes (15).

Therefore, it seems reasonable to hypothesize that combining the analysis of RNFL thickness and optic disc topography in a discriminant formula may enhance the ability to diagnose glaucoma. This study was performed to test the ability of structural parameters, as measured by SLP and CSLO, to discriminate between normal and glaucomatous eyes.

METHODS

After approval of the Ethics Committee of the University of Campinas, all subjects underwent a complete ophthalmologic examination including slit lamp biomicroscopy, applanation tonometry (Goldmann), dilated retinal and optic disc examination, automated perimetry using the Humphrey Visual Field Analyser II (program 24-2, full threshold strategy, Humphrey Systems, Dublin, CA), CSLO using the TOPSS (Laser Diagnostic Technologies, San Diego, CA), and evaluation of the RNFL with the GDx (Laser Diagnostic Technologies), software 1.0.12. Patients were consecutively recruited and categorized into two groups: glaucoma and normal controls. Only one eye per subject was randomly selected if both were eligible.

The inclusion criteria for both groups were visual acuity ≥20/30, refractive error ≤5 diopters, pupillary diameter >2 mm, and two reliable consecutive visual field tests (fixation losses <20%, and false positive and false negative responses <33%) (16). Patients in both groups were excluded if presenting with history of systemic or ocular disease (except glaucoma) that could interfere with optic disc topography, RNFL measurements, or visual field results. Patients who underwent refractive surgery, or showed any significant change in the slit lamp examination that could interfere with the examinations (i.e., corneal opacity, uveitis), were excluded. We also excluded aphakic and pseudophakic eyes, and those with significant cataract – greater than mild lens opacification, according to the Lens Opacity Classification System III (17).

Normal subjects were recruited from volunteers among the medical staff, University members, family and friends of patients. These were excluded if presenting with intraocular pressure (IOP) >21 mmHg, a suspicious disc (localized rim loss, optic disc hemorrhage, cup/disc diameter asymmetry >0.2; the optic disc size was considered when comparing asymmetry between the eyes), or glaucomatous visual field defects (as defined below).

Glaucoma subjects were recruited from the glaucoma service of the University of Campinas. The inclusion criteria were clinical diagnosis of open-angle glaucoma (that is, two or more IOP measurements >21 mmHg, gonioscopy demonstrating open angle and optic disc damage, defined as the presence of at least two of the following characteristics: cup/disc diameter ratio ≥0.6, localized rim loss, disc hemorrhage, or cup/disc diameter asymmetry >0.2, considering the optic disc size, as described above). Furthermore, a typical glaucomatous visual field defect had to be present on at least two reliable visual field examinations. This was defined as the presence of at least two of the following criteria: a cluster of three or more nonedge points, all of which depressed on the pattern deviation plot at a p<5% level and one of which depressed at a p<1% level on two consecutive fields, Glaucoma Hemifield Test outside normal limits, and a corrected pattern standard deviation occurring in less than 5% of normal fields (18).

Patients with glaucoma were classified according to the severity of visual field loss, using the following criteria: 1) early damage: mean deviation (MD) no worse than –6 dB and corrected pattern standard deviation (CPSD) no worse than 1%; 2) moderate damage: MD between –6 dB and –15 dB and CPSD no worse than 1%; 3) severe damage: MD worse than –15 dB or CPSD worse than 1% (8).

Subsequently, a single and experienced examiner (L.M.) outlined the disc margin as the inner margin of Elschnig's ring and obtained the CSLO and SLP images. Room light was kept on and pupils left undilated. The CSLO device obtains three consecutive and independent topographic images, from which it creates an average baseline image. The use of these three images is mandatory and a requirement in order to obtain the analysis. The TOPSS software measures 12 parameters: average disc diameter, total disc area, cup area, cup shape, cup

volume, average cup depth, average disc depth, neuroretinal rim (NRR) volume, NRR area, cup/disc area ratio, horizontal cup/disc ratio, and vertical cup/disc ratio. The use of three images is not a prerequisite in the SLP, but in our study a mean image was obtained from three independent and consecutive 15∞ images. To be included, each image had to satisfy the software's criteria of quality. The SLP variables and their meaning have been described elsewhere (8). The interval between the two visual field tests, CSLO and SLP examinations was not greater than 6 months.

Statistical analysis was performed using the Statistical Analysis System for Windows version 8.1 (SAS Institute Inc., Cary, NC). Receiver operator characteristic (ROC) curves were created for each single CSLO and SLP parameter. The area under each curve was calculated, and cut-off points were selected in order to achieve the best sensitivity/specificity ratio. Subsequently, a multivariate logistic regression analysis was developed for CSLO and SLP parameters separately, and then using parameters derived from both devices. Because age was statistically different between normal controls and glaucoma subjects, it was included as one of the possible variables. A multivariate logistic regression analysis has the same purpose of the discriminant function and allows one to specify how independent variables are entered into the analysis. The goal of this method is to create a formula where one can discriminate between two subsets of populations better than using any single variable entered in the analysis, simplifying to a single result the analysis of a larger number of variables. This method was chosen because our variables did not show normal distribution (Gaussian-like, as measured by the Komogorov-Smirnov test).

RESULTS

A total of 200 individuals, 88 normal and 112 glaucoma patients, were enrolled in the study. The mean age in the glaucoma group (63.6±13.11 years) was significantly higher than the normal controls (47.32±6.03 years) (p<0.001). Thirty-six patients (32.1%) were classified as having early glaucomatous damage, 47 (42.0%) had moderate, and 29 (25.9%) had severe damage. The mean MD for the 112 glaucoma patients was –10.63±7.58 dB. Demographic data are displayed in Table I.

The distribution of the best individual parameters in the diagnosis of glaucoma for each device is shown in Tables II and III. The multivariate analysis including age as a variable resulted in a better sensitivity (Se)/specificity (Sp) ratio compared to individual parameters, both for the CSLO (Se: 90%, Sp: 81%, area under the ROC curve: 0.91, accuracy: 86%) (Fig. 1) and SLP (Se: 87%, Sp: 86%, area under the ROC curve: 0.90, accuracy: 86%) (Fig. 2). Thereafter, we combined parameters derived from CSLO and SLP. The following formula was developed:

$$\pi(x) = \frac{\exp(-59.4 + 67.9 * t1 - 22.2 * t2 + 1.5 * t3 - 1.8 * g6 + 0.2 * g8 - 0.2 * g9 - 30.3 * g12)}{1 + \exp(-59.4 + 67.9 * t1 - 22.2 * t2 + 1.5 * t3 - 1.8 * g6 + 0.2 * g8 - 0.2 * g9 - 30.3 * g12)}$$

TABLE I - DEMOGRAPHIC DATA

	Normal controls	Glaucoma patients	p
Number	88	112	-
Age, yr, mean ± SD*	47.32±6.03	63.6±13.11	<0.001
Male/Female†	35/53	56/56	0.14
White/Black/Asian‡	62/24/02	74/34/04	0.75
Refractive error, diopters§	0.32±0.92	-0.3±2.34	0.01
Eye, right/left‡	49/39	64/48	0.95

*Independent Student t-test; †Fisher's exact test; ‡Chi-square test; §Mann-Whitney U test

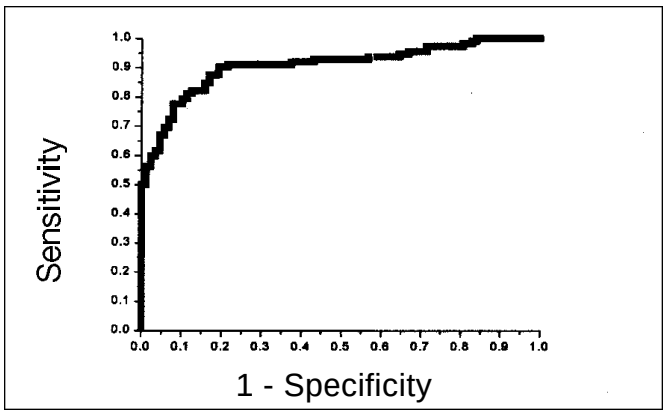

Fig. 1 - Receiver operator characteristic curve for the confocal scanning laser ophthalmoscope multivariate analysis.

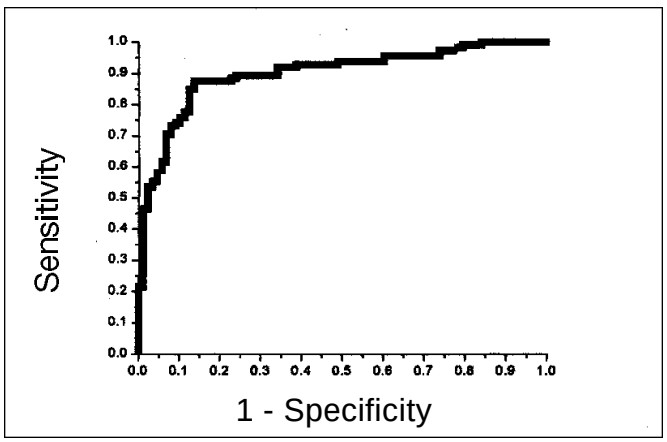

Fig. 2 - Receiver operator characteristic curve for scanning laser polarimeter multivariate analysis.

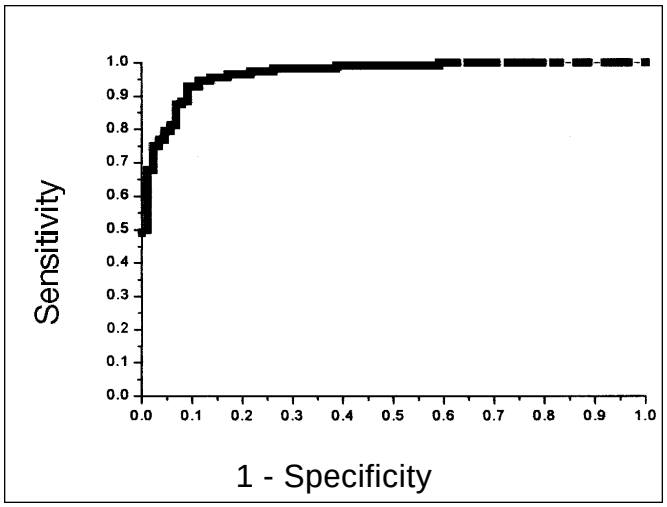

Fig. 3 - Receiver operator characteristic curve for multivariate analysis including confocal scanning laser ophthalmoscope and scanning laser polarimeter.

With: CSLO: t1: average disc diameter; t2: total disc area; t3: cup/disc area ratio.

SLP: g6: ellipse modulation; g8: average thickness; g9: ellipse average; g12: superior integral.

With this analysis, we achieved an area of 0.97 under the ROC curve (Fig. 3). With a cut-off point set at greater than or equal to 0.57 as abnormal (glaucoma), a sensitivity of 93% and a specificity of 91% were observed, with an accuracy of 92%.

DISCUSSION

In our study, CSLO and SLP were combined to assess structural parameters from the optic disc and RNFL. Although they target different components of the eye, studies with glaucoma patients have demonstrated early damage to these structures, even before confirmed visual field loss (3, 4). Furthermore, perimetric damage is only detectable after a certain amount of retinal ganglion cell death (6, 19).

The SLP parameters found to have the best ability in segregating normal controls from glaucoma subjects were the number, maximum modulation, and ellipse modulation (Tab. III). These finding are in accordance with previous studies, where the number was the most predictive single variable in differentiating healthy from glaucomatous eyes (8, 20). Average disc diameter, total disc area, and cup area were the best individual parameters for CSLO in differentiating glaucoma from normal subjects.

The large variability of optic disc and RNFL measurements (14, 21) may influence the examination results, and therefore considerable overlap between individuals with glaucoma and normal subjects may exist when analyzing single parameters derived from these structures. The combination of two or more parameters with discriminant formulas, either for CSLO or SLP, may therefore improve the efficacy of each device. Our findings are in agreement with previous reports, where similar sensitivity/specificity ratios for the diagnosis of glaucoma with discriminant functions were obtained using the SLP (8, 20) or the CSLO (9, 11, 12, 22). Mikelberg and colleagues (12) have employed cup-shape measure, rim volume, and height variation contour to develop their formula, obtaining a sensitivity of 87% and specificity of 84% in the diagnosis of glaucoma. Other authors have achieved similar results with optic disc topography, such

TABLE II - MEAN, RANGE, AND MEDIAN FOR THE BEST CSLO AND SLP PARAMETERS IN THE NORMAL AND GLAUCOMA GROUPS

	Group	Mean ±	Range	Median standard deviation*
CSLO				
Average disc diameter	Normal	1.68±0.19	1.22	1.67
	Glaucoma	1.92±0.22	1.12	1.89
Total disc area	Normal	2.22±0.54	3.75	2.19
	Glaucoma	2.82±0.63	3.32	2.72
Cup area	Normal	0.83±0.46	2.63	0.79
	Glaucoma	1.50±0.68	3.84	1.45
SLP				
The number	Normal	24.28±17.55	81	17
	Glaucoma	58.77±24.99	88	61
Maximum modulation	Normal	1.42±0.47	2.54	1.39
	Glaucoma	0.82±0.38	2.31	0.78
Ellipse modulation	Normal	2.67±0.71	3.60	2.67
	Glaucoma	1.69±0.64	3.35	1.59

CSLO = Confocal scanning laser ophthalmoscope; SLP = Scanning laser polarimeter

TABLE III - CUTOFF POINTS, SENSITIVITY, SPECIFICITY, AND AREA UNDER THE ROC CURVE FOR THE BEST CSLO AND SLP PARAMETERS

	Cut-off point	Sensitivity, %	Specificity, %	ROC
CSLO				
Average disc diameter	≥1.833	64.3	88.6	0.824
Total disc area	≥2.309	84.8	65.9	0.802
Cup area	≥1.192	68.8	85.	0.797
SLP				
The number	≥34.5	79.5	81.8	0.870
Maximum modulation	≤1.115	83.0	76.1	0.842
Ellipse modulation	≤1.845	65.2	88.6	0.831

ROC = Receiver operator characteristic; CSLO = Confocal scanning laser ophthalmoscope; SLP = Scanning laser polarimeter

as Wollstein et al for the HRT (Se: 84.3%; Sp: 84%) (11) or Ahn and Kee (9) for the TOPSS (Se: 89.7%; Sp: 89.1%) in a Korean population. Weinreb and coworkers (8) have developed a linear discriminant formula with three SLP parameters (average thickness, ellipse modulation, and average ellipse thickness), obtaining a sensitivity of 74% and a specificity of 92%.

The idea of combining structural (SLP) and functional data (visual field) in order to enhance the ability to diagnose glaucoma was proposed by Lauande-Pimentel et al (20) (Se: 93%; Sp: 90.1%), who also obtained a linear discriminant function with SLP parameters (Se: 90.4%; Sp: 90.1%). All articles described above reported that discriminant functions achieve better Se/Sp ratio than any single parameter, confirming that joining two or more variables may improve the diagnosis of glaucoma.

Measurements of the RNFL thickness and optic disc topography have demonstrated comparable capacity in distinguishing normal eyes from those with glaucoma (23). We hypothesized that combining the abilities of these instruments may enhance this capability by targeting different structures that are injured early in glaucoma. Greaney and colleagues (23) recently reported improved ability in differentiating healthy individuals from glaucomatous eyes using two different methods to measure the RNFL thickness (SLP and optical coherence tomography) and two other instruments to assess optic disc topography (CSLO with the HRT and optic disc stereophotography scores).

Although they obtained an area under the ROC curve of 0.99 with the combination of 37 parameters derived from these four methods, the clinical usefulness of this finding is limited by the high costs of four different devices and by the time spent by the patients during these examinations. In the present study, the discriminant formula was developed using only one method to evaluate optic disc topography (CSLO with the TOPSS) and another one to determine the RNFL thickness (SLP). Although we used considerably less optic disc and RNFL parameters (n=7) in our analysis compared to a previous article (23), the formula we developed obtained very similar results: an area under the ROC curve of 0.97, a sensitivity of 93%, and a specificity of 91%.

One may criticize the fact that structural parameters (i.e., optic nerve head appearance) were used as inclusion criteria for both normal and glaucomatous groups (24), which could have artificially increased the sensitivity and specificity of the multivariate analysis. Although this is possibly true, we elected to use these criteria in order to avoid the inclusion of suspicious optic discs in the normal population. Furthermore, previous studies evaluating the Se/Sp of structural parameters (optic disc topography, RNFL, or both) have used optic disc appearance as part of the inclusion criteria (7, 8, 20, 22, 25, 26).

Another weakness of this study is related to population probability. Because we included a selected population with more glaucoma patients (112/200, 56%) than expected in an arbitrary sample, this may have falsely increased the sensitivity and decreased the specificity of the device. Furthermore, there was a significant difference in the mean age of both groups, which may have influenced our findings, decreasing the sensitivity and specificity of our discriminant formula, since some of the morphologic parameters examined depend on age. The option for an age-matched control group instead of the inclusion of consecutive individuals would have solved this source of bias.

Despite these limitations, this study was the first one to develop a possible clinically useful method (a discriminant formula) by objectively evaluating two structures that are damaged early in the pathogenesis of glaucoma, therefore enhancing our ability to detect this disease. However, this should be considered a pilot study. The discriminant formula we developed was tested in the same group from where it was derived. The real sensitivity and specificity of these instruments to identify glaucoma subjects in a general population are unknown. Further studies investigating a random population are needed in order to test the validity of the formulas reported herein.

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