EXTENDED REPORT

Comparison of retinal nerve fibre layer thickness and visual field loss between different glaucoma groups

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Background/aims: Scanning laser polarimetry (SLP) uses a confocal scanning laser ophthalmoscope with an integrated polarimeter to evaluate the thickness of the retinal nerve fibre layer (RNFL). The aim of this study was to verify the ability of the SLP to detect differences in RNFL thickness between normal and glaucomatous eyes and between glaucomatous eyes subdivided in groups by the severity of visual field damage.

Methods: This was a cross sectional retrospective study. The charts of 40 healthy subjects and 68 glaucoma patients who underwent complete ophthalmological examination, optic disc stereophotography, peripapillary, and macular SLP imaging were reviewed. The right eye of subjects eligible for the study was enrolled. Only eyes with SLP examinations indicating a minimised effect of anterior segment birefringence based on macular image were included. The ability of retardation parameters to discriminate between healthy and glaucomatous eyes was evaluated. Based on visual field loss, glaucoma patients were subdivided in three subgroups (early, moderate, and severe). RNFL thickness between healthy control group and glaucoma subgroups was compared. RNFL thickness and visual field loss correlation was evaluated.

Results: There was a significant difference in superior and inferior maximum RNFL thickness between normal and glaucomatous eyes ($p<0.001$). With these two parameters, the area under receiver operator characteristic curve was 0.75 and 0.74, respectively. Superior and inferior RNFL thickness was significantly different between healthy control group and all glaucoma subgroups ($p<0.001$) and between glaucoma subgroups ($p<0.05$), except for early and moderate glaucoma subgroups ($p>0.05$). Linear regression showed a weak correlation between RNFL thickness and visual field loss.

Conclusion: These results suggest that once visual field loss is established, smaller reductions in the RNFL thickness detected by SLP are necessary for a given reduction of mean defect value.

Glaucoma is characterised by a progressive degeneration of retinal ganglion cells and their axonal fibres. Retinal nerve fibre layer (RNFL) loss, optic disc cupping and visual field loss can be detected and used to diagnose and monitor this disease. Scanning laser polarimetry (SLP) uses a confocal scanning laser ophthalmoscope with an integrated polarimeter to quantitatively evaluate the thickness of the RNFL.[1] This measurement is based on birefringent properties of the retinal ganglion cell axons that can change the state of polarisation of an illuminating laser beam. The change in polarisation, referred to as retardation, is proportional to the thickness of the birefringent medium and measured to give an index of RNFL thickness. The technology incorporates an anterior segment compensator to neutralise the polarisation effects of the cornea and crystalline lens.[2]

Previous studies found that quantitative measures of the retinal nerve fibre layer with SLP correlate with the visual field loss in patients with glaucoma,[3 4] but the amount of variation explained by the models was relatively modest. One possible explanation may be related to the anterior segment birefringence.

Recent studies have demonstrated that the narrow band corneal compensator used by the GDx scanning laser polarimeter is inappropriately compensating for corneal birefringence in many healthy and glaucomatous eyes.[5 6] Nevertheless, a good number of eyes have anterior segment birefringence well compensated by the instrument.

The purpose of our investigation was to verify, in these eyes, the ability of the SLP (GDx) to detect differences in RNFL thickness between normal and glaucomatous eyes. To study the correlation between RNFL structural damage and visual function, patients with glaucoma were divided in subgroups based on visual field loss and their RNFL thicknesses were compared.

PATIENTS AND METHODS

The charts of 160 glaucoma patients and 100 healthy volunteers examined between January and March 1998 were reviewed. The right eyes from subjects meeting entry criteria were enrolled in this retrospective study. All subjects were between 19 and 84 years old. All eyes included had best corrected visual acuity of 20/20, spherical refraction within plus or minus 5.0 dioptres, and cylinder correction within plus or minus 2.5 dioptres. Eyes with coexisting retinal disease, uveitis, amblyopia, non-glaucomatous optic neuropathy, or other ocular disease that could affect visual field performance were excluded from this investigation.

All participants underwent a complete ophthalmological examination including stereoscopic photographs of the optic nerve and achromatic automated perimetry performed with the Humphrey field analyser (Humphrey Systems, Inc, Dublin, CA, USA), full threshold, program 24-2.

Healthy subjects had no history of ocular disease, surgery, or elevated intraocular pressure (IOP). Their examination revealed IOP less 21 mm Hg (Goldmann applanation tonometry) on more than one occasion, normal optic disc

Abbreviations: CPSD, corrected pattern standard deviation; GHT, glaucoma hemifield test; IOP. intraocular pressure, ; MD, mean defect; RNFL, retinal nerve fibre layer; ROC, receiver operator characteristic; SLP, scanning laser polarimetry

appearance, and normal findings on visual field test. Absence of glaucomatous optic neuropathy was defined as vertical cup/disc asymmetry less than 0.2, cup/disc ratio less than 0.6, and an intact neuroretinal rim without peripapillary haemorrhages, notches, localised pallor, or an RNFL defect. Normal visual field indices were defined as a mean defect (MD) and corrected pattern standard deviation (CPSD) within 95% confidence limits and a glaucoma hemifield test (GHT) result within normal limits. Fixation loss and false positives and false negatives less than 20% characterised a reliable visual field examination.

Glaucomatous optic neuropathy was defined as cup/disc asymmetry between fellow eyes of greater than 0.2, rim thinning, notching, excavation, or RNFL defect.

Patients with glaucoma presented glaucomatous optic nerve damage and associated visual field loss confirmed by a second examination. Visual field defect on the Humphrey field analyser, was defined as GHT result outside the 99% normal limits and/or corrected pattern standard deviation outside the 95% normal limits. Examinations with a ''borderline'' or a ''generalised depression of sensitivity'' result in the GHT test were excluded.

All eyes underwent undilated RNFL measurements obtained with a scanning laser polarimeter (GDx nerve fibre analyser; Laser Diagnostic Technologies Inc, San Diego, CA, USA) by an experienced operator. The technology has been described in detail previously.[1 7] The same operator performed image acquisition in a standardised fashion. The optic disc margin was approximated by a circle or ellipse placed by the operator around the inner margin of the peripapillary scleral ring. A measuring circle or ellipse was then generated by the instrument at 1.75 disc diameters concentric with the margin of the optic disc.

A baseline image was obtained from the mean of three scans accepted by GDx, that yielded a mean pixel standard deviation less than or equal to 8.0 μm.

Recent studies suggest that the narrow band corneal compensator used by the GDx scanning laser polarimeter is inappropriately compensating for anterior segment birefringence in many eyes. Assessment of macular images may indicate which eyes the original fixed corneal compensator would appropriately compensate. In this case, the macular image should be uniform and dark around the fovea and yield a flat macular retardation profile.[8] In this study, one macular polarimetry image was obtained from each subject and evaluated by two experienced examiners. Only eyes that presented a macular image with those characteristics (indicating a minimised effect of anterior segment birefringence) were included.

The original software of GDx provides many variables for analysis. In this particular study, the following parameters were chosen to assess the RNFL thickness: superior maximum (the average of the 1500 thickest pixels in the superior quadrant), inferior maximum (the average of the 1500 thickest pixels in the superior quadrant), temporal median (average of the 1500 median pixels in the temporal quadrant), and nasal median (average of the 1500 median pixels in the nasal quadrant).

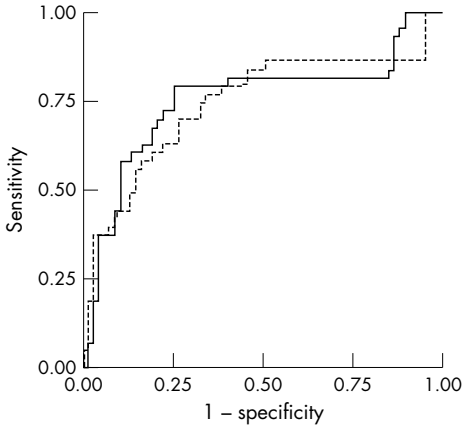

Figure 1 Receiver operating characteristic curve for superior maximum thickness (μm) (solid line) and inferior maximum thickness (μm) (broken line).

Achromatic automated perimetry was performed within 3 months of clinical examination and RNFL thickness determination.

To evaluate differences in RNFL thickness between different stages of glaucoma neuropathy, patients were classified in three subgroups based on MD index of visual field: early, moderate, and severe glaucoma. Early glaucoma was defined by a visual field loss with an MD no worse than −5 dB. Moderate glaucoma was defined by a visual field with an MD value between −5 dB and −10 dB. An MD worse than −10 dB characterised patients with severe visual field loss.

Statistical analysis was performed using commercially available software (JMP; SAS Institute, Cary, NC, and SPSS 10.0; SPSS Inc, Chicago, IL, USA). Student's *t* test was used to evaluate differences in RNFL thickness between normal and glaucomatous eyes. Logistic regression and area under the receiver operator characteristic (ROC) curve were used to assess the ability of SLP variables to differentiate between healthy and glaucomatous eyes. Analysis of variance with the Student-Newman-Keuls test for multiple comparisons was used to test differences in SLP variables within groups. Linear and polynomial regression analysis was performed to evaluate the relation between MD value and SLP RNFL thickness measurements of all subjects.

Table 1 Clinical characteristics of the study population

	Normal (n = 40)	Glaucoma (n = 68)	p Value
Mean age (SD) (years)	44.2 (14.8)	59.9 (14.9)	<0.0001*
Range (years)	19–78	24–84	<0.001*
Sex (male/female)	30/10	35/33	0.02†
Mean visual field MD (SD) (dB)	−0.4 (1.7)	−7.3 (7.1)	<0.0001*
Mean visual field CPSD (SD) (dB)	0.9 (0.7)	5.8 (4.0)	<0.0001*
Superior thickness (SD) (μm)	105.13 (18.92)	76.25 (22.69)	<0.0001*
Range (μm)	71.60–150.40	37.30–153.90	
Inferior thickness (SD) (μm)	97.59 (16.01)	73.25 (20.82)	<0.0001*
Range (μm)	65.10–129.70	32.70–134.20	
Temporal thickness (SD) (μm)	41.62 (14.78)	39.67 (11.85)	NS
Range (μm)	21.00–88.60	14.78–41.62	
Nasal thickness (SD) (μm)	48.02 (12.69)	47.69 (10.21)	NS
Range (μm)	35.10–88.00	29.50–82.90	

*Student's *t* test; †χ^2 test.

Table 2 Superior and inferior maximum retardation parameters and global visual field indexes of normal control group and glaucoma subgroups

	Normal	Early glaucoma	Moderate glaucoma	Severe glaucoma	p Value
Superior maximum (SD) (μm)	105.13 (18.92)	82.44 (25.03)	76.96 (18.14)	64.91 (11.27)	<0.0001†
Inferior maximum (SD) (μm)	97.59 (16.01)	78.52 (20.81)	76.74 (17.04)	61.17 (15.79)	<0.0001†
Mean deviation (SD) (dB)	−0.31 (1.69)	−1.92 (1.87)	−6.81 (1.29)	−17.13 (4.84)	<0.0001†
Corrected pattern standard deviation (CPSD) (SD)	0.95 (0.70)	2.72 (2.38)	7.00 (2.48)	10.04 (2.65)	<0.0001†

†ANOVA and multiple comparisons with Student-Newman-Keuls.
Superior and inferior maximum: significant difference between normal group and each glaucoma subgroup, significant difference between initial and severe glaucoma subgroup and between moderate and severe glaucoma subgroup ($p<0.05$).
MD and CPSD value: significant difference between all pairs.

RESULTS

One hundred and eight eyes (40 normal, 68 glaucomatous) of 108 subjects (65 (60%) female, 43 (40%) male) were enrolled in this investigation. Demographic characteristics of the study population are described in table 1. Patients with glaucoma were significantly older than normal subjects ($p<0.001$). There were statistically significant differences between healthy subjects and glaucomatous groups for superior and inferior maximum thickness ($p<0.0001$), but not for temporal and nasal median thickness (table 2). Using logistic regression analysis, superior maximum and inferior maximum thickness showed a good ability to discriminate between healthy and glaucomatous eyes. Their area under ROC was 0.75 and 0.74, respectively (fig 1). With an arbitrarily selected cut off of lower than 80 μm as glaucoma, sensitivity and specificity of superior maximum were 79% and 75%, respectively. For an arbitrary cut off of 84 μm, sensitivity and specificity of inferior maximum were 63% and 78%.

There was no significant difference in age and sex between glaucoma subgroups ($p<0.05$). Mean superior and inferior maximum thickness of control group and all glaucoma subgroups are presented in table 2.

There was a significant difference in these retardation parameters between patients with early glaucoma and healthy subjects ($p<0.0001$). In the early glaucoma subgroup, superior and inferior maximum mean value were respectively 22.7 μm (21.6%) and 19.1 μm (19.6%) thinner than healthy control group.

Superior and inferior maximum thickness measured in the subgroup of moderate glaucoma were, respectively, 5.5 μm (6.6%) and 1.8 μm (2.3%) thinner than initial glaucoma subgroup. This difference was not significant.

The same retardation parameters measured in severe glaucoma subgroup were, respectively, 12.1 μm (15.2%) and 15.6 μm (20.3%) thinner than moderate glaucoma subgroup ($p = 0.04$).

There was a difference of 20.9 μm in mean RNFL thickness (mean of superior and inferior maximum) between healthy subjects and patients with early glaucoma. This was associated with a difference of 1.61 dB in the mean MD value between these groups. Mean RNFL thickness in severe glaucoma patients was 18.0 μm thinner than patients with early glaucoma. The same groups presented a difference of 10.32 dB in the mean MD value.

Linear regression showed a modest correlation between MD value and mean RNFL thickness (mean of superior and inferior maximum thickness) ($r^2 = 0.24$, $p<0.001$). The same was observed for CPSD value ($r^2 = 0.25$; $p<0.001$). This correlation was slightly, but not significantly, better with a polynomial regression of degree 2 (figs 2 and 3). A parabola fit shows small variations in MD value for higher RNFL thickness measurements and larger differences in MD values for lower RNFL thickness measurements.

DISCUSSION

In this study, we evaluated a particular group of patients who present a better compensation for anterior segment birefringence when using the SLP with fixed corneal compensation. Our results showed an overlap between healthy and glaucomatous eyes in the range of values for all retardation

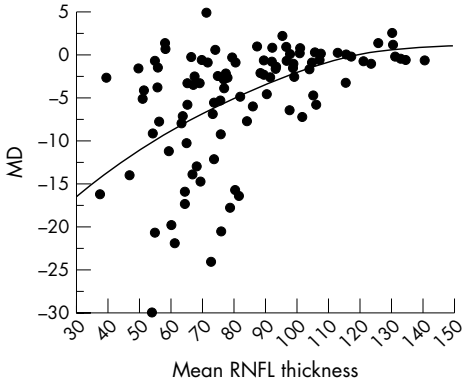

Figure 2 Fitted curve between visual field indexes (MD and CPSD) and mean RNFL thickness (mean of superior and inferior maximum) of all subjects based on a polynomial regression of degree^2.
MD = −17 52862+0 1580892 RNFL −0 001195 (RNFL −84 5458)^2.
CPSD = 11 64816−0 0927809 RNFL +0 0004628 (RNFL −84 5458)^2.
Scatter plot shows small variability of MD and CPSD values for higher RNFL thickness measurements and larger changes in those visual field indexes for lower RNFL thickness measurements ($r^2 = 0.26$; $p<0.001$ for both indexes).

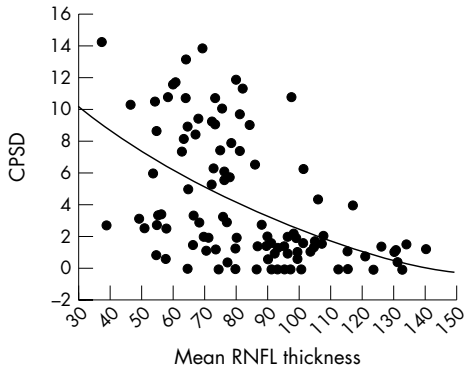

Figure 3 Fitted curve between visual field indexes (MD and CPSD) and mean RNFL thickness (mean of superior and inferior maximum) of all subjects based on a polynomial regression of degree^2.
MD = −17 52862+0 1580892 RNFL −0 001195 (RNFL −84 5458)^2.
CPSD = 11 64816−0 0927809 RNFL +0 0004628 (RNFL −84 5458)^2.
Scatter plot shows small variability of MD and CPSD values for higher RNFL thickness measurements and larger changes in those visual field indexes for lower RNFL thickness measurements ($r^2 = 0.26$; $p<0.001$ for both indexes).

parameters studied. This finding is in agreement with previous studies.[3 9] However, our study showed a good ability to differentiate between healthy and glaucomatous eyes using superior and inferior maximum parameters, differently from other reports.[9 10] The selection of eyes with better anterior segment compensation by the instrument may account for these findings. A recent publication by Greenfield and colleagues[11] observed that correction for corneal polarisation axis improves the ability to discriminate between normal and glaucomatous eyes for five retardation parameters quantifying RNFL thickness. Superior and inferior maximum thicknesses were not reported in their study. Although these are not parameters that have been found to have the best correlation with visual function in other studies[1 9] they were evaluated without considering the corneal compensation issue. In this study we decided to use these two parameters because they may be more directly related to RNFL thickness measurement than other coefficients based on various algorithms (such as ''the number'') which would be of better interest when analysing the relation between structure and function.

The difference in age between normal healthy subjects and patients with glaucoma may be considered a source of bias in the discriminating power of SLP parameters for detection of glaucomatous eyes in this study. However, the amount of influence would be probably small considering the suggested RNFL decay rate between 0.2 μm and 0.38 μm/year.[12]

To study the correlation between RNFL structural damage and visual field loss, we compared differences in RNFL thickness with differences in visual field MD index between groups. We detected a significant difference in RNFL thickness between eyes of healthy subjects and eyes of patients with early glaucoma, but not between early and moderate glaucomatous eyes. By the same time, similar reductions in RNFL thickness were correlated with different reductions in MD value when we observed the comparisons between healthy subjects and patients with early glaucoma and between patients with early and severe glaucoma. These findings suggest that once the visual field loss is established, smaller amounts of RNFL thickness are necessary for a given reduction of MD value.

These observations also help explain the weak linear correlation between mean RNFL thickness and visual field global indexes of all subjects in our study. Because of that we tried an alternative model that does not provide a significant better fit for our scatter plot, but may highlight the variability of the relation between structure and function. The scatter plot shows small differences in MD value for higher RNFL thickness measurements and larger variations for thinner measurements, suggesting an important change in the relation between these two variables with increasing visual field defect and RNFL thickness reduction. CPSD index shows the same correlation. Similar findings were observed by Kwon and co-workers.[4] The authors suggested a bilinear correlation with great variability between SLP RNFL measurements and visual field parameters.

Our results are also in agreement with histological studies. Quigley and co-workers[13] showed that up to 40% to 50% of nerve fibres could be lost in the absence of a field defect. A later study with a larger number of eyes showed that a reduction of at least 25% to 35% in retinal ganglion cell population is associated with statistical abnormalities in automated perimetry.[14] This same study also provided a modest linear correlation between the MD value and the total axon number estimate in each eye. The same was observed for CPSD index. One experimental glaucoma study in monkeys observed a non-linear relation between the proportional losses of ganglion cells and visual sensitivity, measured with either white or coloured stimuli.[15]

There are inherent limitations of a cross sectional study to examine the relation between structure and function.[3] The variability of the number of nerve fibres in the normal optic nerve contributes for a difficult correlation between visual field loss and RNFL thickness damage when studying different patients. In addition, it is possible that different glaucoma patients would need to lose different amounts of retinal nerve fibres to produce similar visual field defects. One might expect, therefore, that the strength of this association could vary depending on the glaucoma patients included in the study and the severity of their disease.[3]

Our study was able to give an estimative of the relation between visual field performance and RNFL thickness variation measured by SLP among normal subjects and glaucoma patients in different stages of the disease. It seems that once the visual field loss is established, smaller amounts of RNFL thickness are necessary for a given reduction of MD value. Future prospective longitudinal studies evaluating changes in visual field performance and RNFL thickness in the same subjects may confirm our findings and give more details about this relation. Although a new version of GDx is available, the instrument with fixed compensator is still being used by various glaucoma specialists and general ophthalmologists around the world. Properly selected images obtained with this instrument may still reveal important information about the relation between structure and function in glaucoma damage, especially from longitudinal evaluation.

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