Use of the GDx to detect differences in retinal nerve fibre layer thickness between normal, ocular hypertensive and early glaucomatous eyes

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CLINICAL STUDY

Abstract

Purpose **The GDx is a scanning laser polarimeter that has been developed to allow the quantitative analysis of retinal nerve fibre layer (RNFL) thickness. The purpose of this study was to determine whether differences in the RNFL thickness between normal, ocular hypertensive and glaucomatous eyes could be detected using the GDx.**

Methods **RNFL analysis was carried out using the GDx on 33 normal, 145 ocular hypertensive (OHT) and 44 glaucomatous (POAG) eyes. The inclusion criteria for entry into the study did not include the clinical appearance of the RNFL or optic disc, thus eliminating an important source of selection bias. The Kruskal–Wallis one-way analysis of variance was used to determine whether any significant differences existed among the groups in mean total and quadrantic RNFL thickness. When significant differences were found, specific inter-group analysis was carried out using the Mann–Whitney *U*-test.**

Results **Significant differences in RNFL thickness were found for the mean total, superior and inferior quadrant values between normals and OHT eyes as compared with POAG eyes. No significant differences were found for these values between the normal and OHT eyes.**

Conclusion **Analysis of RNFL thickness using the GDx was able to detect differences between POAG eyes compared with normal and OHT eyes, although there was considerable overlap between groups. Further assessment of the technique is required to determine whether it may be useful in screening for the presence of early glaucomatous damage.**

Key words GDx, Glaucoma, Ocular hypertension, Retinal nerve fibre layer

Several authors have demonstrated that retinal nerve fibre layer (RNFL) defects can precede optic disc and visual field change by several years, and may be the earliest sign of glaucomatous damage.[1–4] Current clinical techniques of RNFL examination, such as slit-lamp fundal examination under red-free light and analysis of black and white photographs, are limited in providing mainly qualitative assessment that requires a moderate degree of observer experience. Scanning laser polarimetry is a technique that has been developed with the aim of providing quantitative information on RNFL thickness in specific regions of the peri-papillary fundus.

The GDx is a scanning laser polarimeter developed by Laser Diagnostic Technologies (San Diego, CA). The principles of scanning laser polarimetry have been described elsewhere,[5,6] and will only be outlined here. The technique depends upon the birefringent qualities of the RNFL, whereby the polarisation of light is altered by its passage through the nerve fibres. The degree of change of polarisation is altered in proportion to the depth of the RNFL, and is detected by an in-built polarimeter. Change in polarisation or retardation is then converted into a topographical map of RNFL thickness measurements, calculated by the GDx software.

Potential advantages of this technique for the examination of the RNFL over photographic techniques include the following: no pupillary dilatation is required, image acquisition is relatively unaffected by the presence of moderate media opacities, and quantitative image analysis may be done 'on the spot'. There have been numerous previous studies that have demonstrated the use of the first- and second-generation nerve fibre analysers to discriminate between ocular hypertensive (OHT), glaucoma (POAG) and normal subjects,[5–7] and these will be discussed later. A major criticism of many studies assessing techniques to measure optic

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Table 1. *Mean age (SD) and mean optic disc areas (SD) of groups*

Subject group	Mean (SD) age (years)	Range (years)	Mean (SD) disc area (mm^2)
Normal	65.2 (8.0)	45–78	1.77 (0.35)
OHT	64.3 (10.0)	38–93	1.83 (0.48)
POAG	68.0 (12.0)	36–85	1.77 (0.28)
p value (ANOVA)	0.42		0.59

OHT, ocular hypertension; POAG, primary open angle glaucoma.

disc and RNFL parameters is the inclusion of subjects on the basis of their clinical optic disc or RNFL appearance.[8] Some previous studies investigating the use of scanning laser polarimetry in POAG and OHT patients have therefore been flawed by this source of selection bias. Therefore, the main purpose of this study was to determine the ability of the GDx to detect differences in the RNFL thickness between these groups of subjects who were not selected on the basis of optic disc and RNFL appearance.

Materials and methods

Inclusion criteria for subjects within each group were as follows:

Normal subjects

1. Intraocular pressure (IOP) on Goldmann tonometry < 21 mmHg on at least two separate occasions, measured by the same operator.
2. Normal 24-2 Humphrey visual fields with an AGIS score of 0 (Advanced Glaucoma Intervention Study)[9] on at least two separate occasions.
3. No family history of OHT or POAG.
4. Age > 35 years.

OHT patients

1. IOP on Goldmann tonometry > 22 mmHg and ≤ 35 mmHg on at least two separate occasions.
2. Normal 24-2 Humphrey visual fields with an AGIS score of 0 on at least two separate occasions.
3. Age > 35 years.

POAG patients

1. Initial untreated IOP on Goldmann tonometry > 21 mmHg on at least two separate occasions.
2. Reproducible visual field defects on at least three 24–2 Humphrey visual fields. All visual field defects were classified as showing early glaucomatous change with AGIS scores of 1–5.
3. Age > 35 years.

Clinical optic disc and RNFL appearance on slit-lamp biomicroscopy were not inclusion criteria for any of the subject groups.

One eye per subject was entered into the study. When both eyes fitted the above criteria, then the study eye was chosen at random. Thirty-three normal eyes, 44 POAG eyes and 145 OHT eyes were included in the analysis.

All imaging was performed through an undilated pupil. Three good-quality 15° by 15° images of the RNFL and optic disc were obtained for each eye, by one of two experienced technicians. The individual images were all analysed by a single experienced operator (D.S.K.). A contour line was fitted as closely as possible to the disc edge, using the mouse. The RNFL thickness at 1.5 disc diameters from the centre of the optic disc was then analysed using GDx software in four quadrants: superior, inferior, temporal and nasal. The software also calculated a total circumferential RNFL thickness. The total and quadrantic values for all three images per eye were then averaged to produce a mean value and this was used in the final analysis. Histogram representation demonstrated skewed data and non-parametric tests were therefore used in the statistical analysis. The Kruskal–Wallis one-way analysis of variance was used to determine whether there were any overall differences between the groups in each of the quadrantic and total RNFL thickness values. Further specific inter-group analysis was performed using the Mann–Whitney *U*-test.

The mean ages of the three groups were calculated and compared using ANOVA analysis. Optic disc area measurements were also obtained for each individual from image analysis performed at the same time as the GDx examination, using the Heidelberg Retina Tomograph (HRT, Heidelberg Technologies, Germany). This is a scanning laser ophthalmoscope with built-in software which both images and analyses optic disc parameters to give quantitative values of area and volume. ANOVA analysis of this data was performed to determine whether any inter-group differences in optic disc size existed, as this would influence the RNFL thickness values obtained. Three optic disc images of the study eye were acquired through an undilated pupil, and a mean topography was generated by HRT software version 2.01. The optic disc edge was delineated using a mouse-drawn contour line, and the software was used to automatically calculate the optic disc area, to give a direct measure of optic disc size.

Results

The mean ages and optic disc size for each of the three groups are summarised in Table 1. No significant differences were found between the groups.

Table 2. *Results of the Kruskal–*Wallis one-way analysis of variance for total and quadrantic measurements

Region of RNFL measured	χ^2 value	*p* value
Total	14.0	= 0.001
Inferior	25.6	< 0.001
Superior	10.4	= 0.006
Nasal	2.0	= 0.360
Temporal	2.1	= 0.344

RNFL, retinal nerve fibre layer.

Table 3. *Results of the Mann–Whitney* U*-test comparing OHT, POAG and normal eyes*

Region of RNFL measured	OHT eyes Median (interquartile range) μm	*p* value	POAG eyes Median (interquartile range) μm	*p* value	Normal eyes Median (interquartile range) μm
Total	64.1 (58.6–71.7)	< 0.001	53.2 (53.2–63.3)	< 0.001	65.0 (60.2–73.4)
Inferior	76.1 (64.8–85.7)	< 0.001	63.7 (55.5–72.4)	< 0.001	76.2 (67.6–87.5)
Superior	67.7 (60.7–67.7)	< 0.001	60.6 (54.2–66.6)	< 0.001	72.5 (62.5–81.3)
Nasal	51.5 (46.5–56.7)	= 0.106	48.1 (44.9–55.2)	= 0.138	50.7 (47.0–58.3)
Temporal	45.6 (39.9–54.5)	= 0.393	44.3 (37.0–52.2)	= 0.885	42.7 (37.6–50.9)

The Kruskal–Wallis test demonstrated significant inter-group differences in the total, superior and inferior values of RNFL thickness (Table 2).

Using the Mann–Whitney *U*-test, the following specific inter-group differences were found (Table 3):

1. RNFL thickness was significantly reduced in the POAG eyes compared with the normal eyes for the total, superior and inferior quadrantic values.
2. RNFL thickness was significantly reduced in the POAG eyes compared with the OHT eyes for the total, superior and inferior quadrantic values.
3. No significant differences were found between the normal and OHT group for the total or each of the quadrantic RNFL thickness values.

Discussion

Our results have demonstrated that the relatively new technology utilised by the GDx is able to detect differences between glaucomatous eyes as compared with normal and OHT eyes that were initially grouped on the basis of visual field and IOP characteristics. Our study has therefore eliminated the selection bias that has influenced the results from other studies that have included subjects on the basis of their optic disc and RNFL appearance.[5,7,10]

A study by Tjon-Fo-Sang *et al.*[6] compared the RNFL thickness obtained using the Nerve Fibre Analyser I (a first-generation machine) in normals and OHT subjects with similar characteristics to our own group and found significant differences in the mean superior and inferior values, in contrast to our results. They did, however, also find a large degree of overlap between the groups, and this has been confirmed by later studies using the GDx.[11–13] We did not find any difference in the RNFL thickness values between our normals and OHT groups, despite the well-recognised fact that optic disc and RNFL damage pre-date perimetric change.[2,14,15] The GDx may therefore be limited in its ability to identify early structural damage in those subjects at risk of developing glaucoma.

Our study did not set out to determine the relative specificity and sensitivity of the technique, and the considerable degree of overlap found between groups of subjects would limit the value of this. Another study by the Dutch group, however,[16] specifically addressed the issue of specificity and sensitivity and found surprisingly high values of 93% and 96% respectively. These results, however, have not been reproduced, and may have been affected by technician observer bias (H. Lemij, personal communication to R.A.H., Gullstrand meeting, Stockholm, May 1999). The upgrade in software used by the new-generation GDx machine has limited the influence of such bias on the acquisition of RNFL images.

A more recent study[12] has investigated the ability of the GDx to detect glaucomatous damage, and produced more realistic figures for specificity and sensitivity of 62% and 82% using the GDx software, rising to 74% and 92% using the authors' best discriminant parameter combination. Overlap of values between groups remains the largest obstacle to the use of this tool in population-based screening.

Previous studies[17,18] have found a progressive decline in RNFL thickness values with increasing age, the loss ranging from 0.2 μm to 0.38 μm per year. The mean ages of our subject groups were very similar and it is unlikely that this was a factor influencing our results, but age should be taken into account when individual data are analysed.

We compared only the basic mean quadrantic and total RNFL thickness values in our analysis. Other groups have found analysis of a combination of parameters such as superonasal and inferonasal ratios,[13] and 'modulation' parameters[11] (superior or inferior values minus the average minimum of values in temporal and nasal quadrants) to have greater discriminating ability. Further studies are needed to determine which are the most useful parameters to differentiate between normals, OHT and glaucoma patients, and we are currently carrying out work on larger numbers of subjects included with our same criteria to determine levels of specificity, sensitivity and discriminant ability.

Good reproducibility[7,19,20] of the technique may allow use of this system for longitudinal studies, and preliminary work from our group is promising.[21]

In summary, we have demonstrated that the GDx may detect differences in RNFL thickness between POAG patients as compared with OHT and normal subjects not previously selected on the basis of optic disc and RNFL criteria. The technique shows promise in the detection of early glaucomatous damage but requires further validation before it can be of value in the clinical setting.

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