CHAPTER 7

Sensitivity and specificity of new GDx parameters

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Submitted for publication

Abstract

Purpose The GDx is a scanning laser polarimeter that assesses peripapillary nerve fiber layer thickness. In addition to the 14 existing outcome parameters, 4 new parameters have been described recently: the Ellipse Standard Deviation (ESD), the Normalized Superior Area (NSA), the Normalized Inferior Area (NIA), and the Discriminant Analysis (DA). The aim of this study was to investigate the sensitivity and specificity of these 4 new parameters.

Methods Only one randomly selected eye of 263 healthy volunteers and 241 glaucoma patients was considered. The healthy group was randomly divided into a reference set (n=132) to calculate the 10th percentile of the normal distribution and a test set (n=131) to calculate the specificity against these newly established cut-off points. Sensitivity was calculated for all glaucoma patients (n=241) and again for three separate subgroups: early glaucoma (n=90), moderate glaucoma (n=93) and advanced glaucoma (n=58).

Results When the 10th percentile of the normal distribution was used as a cut-off point, the sensitivity and specificity pairs of the new parameters were 61.8 & 87.6%, 61.8 & 89.1%, 50.2 & 92.2% and 72.6 & 95.3 % for the ESD, NSA, NIA and the DA, respectively. The area under the ROC curve was 0.86, 0.86, 0.87 and 0.90, respectively. Among the existing parameters, the Number discriminated best (sensitivity and specificity: 76.8 & 89.1%, respectively; area under the ROC curve: 0.90). When compared to the Number, the DA was equally good, whereas the other three new parameters performed statistically significantly worse. In general, the area under the ROC curve increased from early to moderate to advanced glaucoma.

Conclusions The new GDx parameters discriminated well between normal subjects and glaucoma patients. None of the new parameters discriminated better than the Number.

Key words: scanning laser polarimetry, GDx, sensitivity, specificity, parameters.

Introduction

The GDx (Laser Diagnostic Technologies, San Diego, CA) is a scanning laser polarimeter that assesses nerve fiber layer (NFL) thickness in the peripapillary retina. The technology discriminates well between normal subjects and glaucoma patients.[1-3] A detailed description of the GDx has been published elsewhere.[4-6] In short, a beam of polarized laser light is sent through the retinal NFL. As the light passes through the form-birefringent NFL, a phase shift called retardation occurs, which is thought to be linearly correlated with NFL thickness, as has been shown in a monkey model.[7] The instrument compensates for retardation arising from the cornea on the assumption that the corneal polarization axis (CPA) is oriented 15 degrees nasally downward. In patients who have a different CPA, this compensation may be inadequate.[8] The peripapillary retina is scanned, and a retardation image of 256x256 pixels is constructed. An operator centers a circle or an ellipse on the optic nerve head, and a 10-pixel wide band with an inner margin of 1.75 times the diameter of the cir-

cle or ellipse is added automatically. The NFL thickness under the band is displayed separately in a so-called double-hump graph. Both the retardation image and the double-hump graph allow a quantitative assessment of the retinal NFL.

For a quantitative approach to the retardation image, several automated parameters are available to the user. For example, the superior maximum parameter averages the 1500 thickest pixels in the 120 deg superior sector, and reflects the thickness of the superior nerve fiber bundle. Since the introduction of the GDx, 14 standard parameters have been available. These include a parameter called 'the Number', which is a summary parameter calculated by a proprietary algorithm, that has been developed with the help of a neural network.

Over the past few years, several authors have developed new parameters, to better discriminate between normal subjects and glaucoma patients. Four of these have been examined in this paper. The Ellipse Standard Deviation (ESD), developed by Choplin *et al.*,[3] is the standard deviation around the mean of the values contained in the measuring ellipse. The Normalized Superior Area (NSA, in mm^2) developed by Xu *et al.*,[9] is the area under a 90 deg sector of the double hump graph with the highest retardation in the superior region. The Normalized Inferior Area (NIA, in mm^2) is defined likewise, only for the inferior region. The fourth parameter is called the Discriminant Analysis (DA), which is identical to the Linear Discriminant Function developed by Weinreb *et al.*[2] It is calculated by an algorithm that uses three existing parameters: average thickness, ellipse modulation and ellipse average. The exact definitions of the four new parameters, as provided by the manufacturer, are presented in the appendix.

To date, these four parameters have not been formally tested on a large group of patients by others than their inventors. We have calculated the sensitivity and specificity of these parameters using data of 241 glaucoma patients and 263 control subjects. For comparison, the sensitivity and specificity values of the 14 existing parameters have been added. To facilitate comparison with other reports, we have included the area under the ROC curve (AUROC) for every parameter. We have also stratified our data for patients with early, moderate and advanced glaucoma.

Methods

Measurement procedures A GDx measurement trial for one eye consisted of taking as many images as needed that yielded 3 high quality ones. High quality was defined as good focus, centered optic disc, equal image illumination in all sectors and the absence of motion artifacts. The 3 images were then aligned and converted by the software into one 'mean image'. For this study we used software version 2.0.09. During all measurements, we saw to it that patients had their heads as upright as possible. Pupils were undilated and ambient lights were left on. Three different experienced operators imaged all subjects on the same instrument within a time period of 2 years. The glaucoma patients were all examined twice within a six-week period; only the data from the second visit was considered.

The following GDx settings were used for our study: the entire image was automatically divided into 4 sectors centered on the optic disc (superior 120°, inferior 120°, nasal 50° and temporal 70°). Our operators then positioned a circle on the margin

of the optic nerve head: the optic disc circle. The circle diameter equaled the largest disc diameter. Instead of using a circle, others prefer to fit an ellipse to the optic disc. We used a circle to obtain measurements that were, in principle, at the same distance from the optic disc center in all sectors. We think this is important, notably to compare ratio and ellipse parameters across subjects. Using a circle rather than an ellipse is not a prerequisite for obtaining the new parameters. After the circle was positioned, the software automatically displayed a green measurement band. This band was 10 pixels wide with an inner circle of 1.75 times the diameter of the optic disc circle. The 14 standard parameters relate either to the pixels under the measurement band, or to those peripheral to it. The data was subsequently exported into a statistical software package (SPSS version 9.0, SPSS Inc., Chicago, IL). A special version of the software that also calculates and exports the 4 new parameters was kindly provided to us by the manufacturer.

Subjects Originally, 272 healthy volunteers were recruited mainly from the hospital staff, their friends and relatives, and spouses of patients. They met the inclusion criteria of: Caucasian ethnic origin, age between 20-80 years, best corrected visual acuity of 20/25 or better, intraocular pressure (IOP) <=21 mm Hg, a normal appearance of the optic nerve head and normal visual fields (Humphrey Field Analyzer 24-2 full threshold program). Exclusion criteria were: diabetes, systemic hypertension requiring medical treatment, any ocular history, a vertical cup/disc ratio of 0.6 or higher, and asymmetry of greater than 0.2 cup/disc ratios between the two eyes. Refractive error was not a selection criterion as long as an image was of high quality. Nine of the recruited volunteers (3.3%) were unsuitable for GDx imaging due to either a very large zone of peripapillary atrophy under or outside the measurement band, or a tilted disc yielding an unreliable GDx scan. In the end, reliable images of high quality could be obtained in 263 subjects (96.7%).

We recruited 255 consecutive glaucoma patients from our glaucoma clinic. The gold standard that separated the normal subjects from the glaucoma patients was the clinical diagnosis of glaucoma. This diagnosis was established by one of our three glaucoma specialists on the basis of a reliable and repeated abnormal visual field (Humphrey Field Analyzer 24-2 full threshold program) that matched the glaucomatous appearance of the optic disc. A visual field exam was classified as reliable when it met the criteria described by Anderson,[10] and as abnormal when the glaucoma hemifield test was outside normal limits. Other inclusion criteria were Caucasian ethnic origin and age between 20-80 years. Exclusion criteria were diabetes, systemic hypertension requiring medical treatment, any ocular history other than glaucoma or any ocular surgery. IOP was not among the selection criteria for the glaucoma patients. Of all recruited patients, 14 (5.5%) were unsuitable for GDx imaging due to a very large zone of peripapillary atrophy outside the measurement band (13 patients), or due to an inability to fixate (1 patient). In the end, reliable images of high quality could be obtained in 241 (94.5%) glaucoma patients.

IRB/ Ethics Committee approval was obtained for this study. Written informed consent was required from all participants after the nature of all procedures had been fully explained. Normal subjects were selected so that six 10-year cohorts ranging

from 20 to 80 years would be represented. We recruited extra control subjects in the 50-60 and 60-70 cohort to better match the expected age distribution in our glaucoma patients. Demographic data of the normal subjects and of the glaucoma patients has been summarized in table 7-1.

Statistical methods From all normal subjects, only one randomly selected eye per subject was used for analysis. If a glaucoma patient had unilateral glaucoma, that eye was selected for analysis. In case of bilateral disease, one eye was selected at random. Next, the group of normal subjects (n=263) was randomly divided into a reference set (n=132) to establish normative values for all parameters, and a test set (n=131) for calculating the specificity. To obtain approximately 90% specificity, we set the following criteria. An abnormal 'the Number' parameter was defined as a value above the 90th percentile of the reference set. An abnormal symmetry parameter was defined as a value above the 95th percentile or below the 5th percentile of the reference set. All other parameters, including the four new parameters, were defined as abnormal when their value was below the 10th percentile. With these criteria, we determined the specificity per parameter in the test set. With the same criteria, we determined the sensitivity per parameter in the glaucoma group. In addition, we calculated the sensitivity for separate glaucoma subgroups. Three groups were defined based on the values of their mean deviation (MD) on visual field testing: the early glaucoma group (MD>-6 dB), the moderate glaucoma group (MD<-6 dB but >-15 dB) and the advanced glaucoma group (MD <-15 dB). The specificities in the various subgroups were identical to the specificity in the 'all patients' group, since the same group of control subjects was used.

In addition to the sensitivity and specificity values, ROC curves were constructed for every parameter. In an ROC curve, sensitivity is plotted on the y-axis against 1-specificity on the x-axis. We also calculated the area under the ROC curve (AUROC) for every parameter and for the three glaucoma subgroups separately.

In the 'all patients' group, we tested the AUROC values of the four new parameters against the best two existing parameters for statistical significance. To that end, we used a paired test described by DeLong *et al.*,[11] with the level of statistical significance set at $\alpha = 0.05$. To assess whether the AUROC values of all parameters increased statistically significantly from early to moderate to advanced glaucoma, a Jonckheere-Terpstra non-parametric test was used with the level of statistical significance set at $\alpha = 0.05$.

Results

All four new parameters discriminated well between normal subjects and glaucoma patients. When all glaucoma patients were considered together, the AUROC values for the ESD, NSA, NIA and the DA were 0.86, 0.86, 0.87 and 0.90, respectively. This data has been summarized in table 7-2, together with AUROC values of the existing parameters. All AUROC values are given again for the three glaucoma subgroups. In general, the AUROC values increased with the severity of glaucoma ($p<0.001$). Sensitivity and specificity values have also been given. The specificity values related to the same group of normal subjects and have thus been presented only once.

In the 'all patients' group, the AUROC value of the DA was higher than that of the maximum modulation (p=0.0059) but not higher than that of The Number (p=0.91; Table 7-3). In the same group, the AUROC values of the ESD, NSA and NIA were not statistically significantly higher than the AUROC value of the maximum modulation. They were statistically significantly lower than the AUROC value of the Number.

Discussion

We have calculated the sensitivity, specificity, and AUROC values for four newly proposed GDx parameters. Their high AUROC values (0.86-0.90) confirmed that they discriminate well between normal and glaucomatous eyes. When compared to the best existing single parameter (maximum modulation), the DA performed better whereas the other 3 new parameters were equally good. When compared to The Number, the DA was equally good, whereas the other 3 new parameters performed worse.

We speculate that feeding the ESD, NSA and the NIA into another neural network to generate a new algorithm for an updated the Number will further increase its ability to distinguish normal from glaucomatous eyes. The DA is perhaps less likely to contribute to such a new algorithm because it is computed from three existing parameters that are already used by the current algorithm of the Number.

The AUROC value for the DA was 0.90 in our study population. This was in agreement with the value of 0.89 found by Weinreb *et al.*,[2] who evaluated only patients with early to moderate glaucoma. Subsequent studies from the same group report values of 0.85 and 0.79, respectively.[12,13] In our study population, the DA discriminated as well as the Number.

The AUROC value for the NSA and NIA was 0.86 and 0.87, respectively, in our population. The group that developed the NSA and NIA tested these parameters on a separate, screening population and found slightly higher values (0.92 and 0.91, respectively) than we did.[14]

We have excluded patients with systemic hypertension from our study because we assumed that (subclinical) retinal ischaemia might occur in those patients, potentially leading to secondary degeneration of the retinal nerve fiber layer, thereby introducing bias. The exclusion of patients with hypertension may limit the validity of our results to a normotensive population. By excluding one kind of bias, a new kind of selection bias may have been introduced because relatively more patients might have been excluded from the glaucoma group. It would be of interest to investigate whether patients with hypertension have different nerve fiber layer characteristics as measured with the GDx than patient with normal blood pressure. Also among the selection criteria was a glaucomatous appearance of the optic disc for inclusion in the glaucoma group. It is possible that this requirement introduced a bias towards increased sensitivity in our analysis.

Age may confound trials that compare NFL thickness between normal and glaucomatous eyes, because NFL thickness is inversely correlated with age.[4,6,15,16] Although our normal population was, on average, somewhat younger than the glaucoma population, age is unlikely to have introduced any bias in our study: we determined age dependent nor-

mal values in a large group of subjects, ranging widely in age. The age range of our glaucoma population sat well within the age range of our normal subjects.

The instrument compensates for retardation arising from the cornea assuming a corneal polarization axis (CPA) of 60 nanometer at an orientation of 15 degrees nasally downward. In eyes with a different CPA, this compensation may be inadequate.[8] A better compensation will probably affect the retardation values and all derived parameters, but the extent of this effect remains to be investigated.

Our study has confirmed previous studies that the GDx allows better discrimination between normal subjects and glaucoma patients with more advanced disease. The clinical significance of this intuitive result has yet to be determined in various settings, such as screening programs and general ophthalmic clinics, where the adopted criteria may be tailored to specific clinical needs.

Appendix Definition of new GDx Parameters

The Ellipse standard deviation (ESD) Originally called Intra Ellipse Sector Variability.[3] It is the standard deviation around the mean of the values contained in the measuring ellipse. The unit of measure is microns. It is a measure of the variability of the measurements contained in the ellipse and an indirect measure of the "peak to trough" difference and thus another modulation parameter. The mean thickness is determined from the measurement points along the ellipse. That value is subtracted from each point along the ellipse giving the standard deviation for each point. The deviations are totaled giving the ellipse standard deviation. Normal eyes, having higher superior and inferior peaks than glaucoma patients, show the greatest variability and hence the highest ellipse standard deviation values.

The Normalized Superior Area (NSA) and the Normalized Inferior Area (NIA). Based on the ReModS and ReModI parameters by Xu et al.[9] The software evaluates the temporal 90° of the ellipse to find the lowest temporal thickness value. The software then evaluates the remaining 270° to find the lowest nasal thickness value. These two values are then averaged to determine a baseline value. Next, a best-fit algorithm is applied to determine which 90° along the ellipse (between the previously described temporal/nasal points) contain the thickest superior and inferior RNFL to calculate the Normalized Superior Area and Normalized Inferior Area. The positions for these superior and inferior 90° sectors are not fixed. The baseline value is then subtracted from the values contained in the 90° superior and inferior ellipse sectors. These integral (area) values are expressed in mm^2 and are calculated by measuring the thickness of the nerve fiber layer (above the baseline) at each point of the ellipse along the entire 90° sector. These values are totaled. A high value represents high modulation of the double-hump TSNIT pattern as seen in normal patients.

Discriminant Analysis (DA) Originally called Linear Discriminant Function (LDF).[2] It is calculated by the following algorithm: -4.442655 – (0.156 x Average Thickness) + (0.935 x Ellipse Modulation) + (0.183 x Ellipse Average). The DA has no unit of measure. Positive values are within normal limits and negative values are outside normal limits.

Table 7-1. Demographic data of all participants

		n	Mean Age (SD)	OD:OS	MD (SD)
Normal subjects	Reference set	132	51.5 (16.7)	60:72	
	Test set	131	49.8 (16.1)	73:58	
Glaucoma subjects	All patients	241	62.4 (10.2)	121:120	-10.4 (7.3)
	Early	90	63.3 (9.0)	45:45	-3.5 (1.8)
	Moderate	93	62.0 (11.1)	43:50	-10.4 (2.7)
	Advanced	58	61.7 (10.3)	33:25	-20.9 (4.8)

Demographic data for all 263 normal subjects (for the reference set and the test set separately), and for all 241 glaucoma subjects (for early, moderate and advanced glaucoma separately). Presented are: number of subjects per group (n), their mean age in years with the standard deviation in parentheses, the ratio of right versus left eyes (OD:OS), and the average of the mean deviation on visual field testing (MD) in decibels (dB) with its standard deviation (SD) in parentheses.

PARAMETER			ALL PATIENTS		EARLY		MODERATE		ADVANCED	
	unit	Spec	Sens	AUROC	Sens	AUROC	Sens	AUROC	Sens	AUROC
ESD	μ	87.6	61.8	.86	40.0	.80	68.8	.88	84.5	.94
NSA	mm^2	89.1	61.8	.86	48.9	.80	61.3	.87	82.8	.94
NIA	mm^2	92.2	50.2	.87	28.9	.81	53.8	.89	77.6	.95
DA		95.3	72.6	.90	56.7	.84	77.4	.92	89.7	.98
The Number		89.1	76.8	.90	65.6	.84	77.4	.92	93.1	.98
Max Modulation		90.7	61.4	.85	47.8	.78	64.5	.85	77.6	.92
Inferior Ratio		91.5	55.6	.82	40.0	.75	60.2	.84	72.4	.90
Ellipse Mod		90.7	58.5	.82	44.4	.76	59.1	.82	79.3	.91
Superior/Nasal		95.3	36.9	.82	23.3	.77	35.5	.83	60.3	.89
Superior Ratio		90.7	45.6	.79	31.1	.72	44.1	.80	70.7	.90
Inf. Maximum	μ	87.6	43.2	.75	31.1	.68	39.8	.76	67.2	.85
Inferior Average	μ	89.9	44.0	.74	28.9	.65	46.2	.77	63.8	.83
Superior Average	μ	83.7	49.0	.74	41.1	.80	49.5	.75	60.3	.82
Sup Maximum	μ	87.6	37.3	.74	26.7	.67	33.3	.74	60.3	.83
Ellipse Average	μ	87.6	45.6	.71	33.3	.64	49.5	.72	58.6	.79
Superior Integral	mm^2	87.6	36.1	.69	28.9	.62	30.1	.70	56.9	.76
Average	μ	88.4	27.8	.65	18.9	.59	29.0	.65	39.7	.72
Symmetry		89.9	21.6	.53	22.2	.54	20.4	.49	22.4	.55

All investigated parameters are listed: the top 4 parameters are: the Ellipse Standard Deviation (ESD), the Normalized Superior Area (NSA), the Normalized Inferior Area (NIA) and the Discriminant Analysis (DA). All 14 existing parameters are given below, ranked by their AUROC values in the 'all patients' group. The unit of measure is given where applicable. Both sensitivity and specificity values are given in percentages. The sensitivity and specificity for every parameter is first presented for the group of 'all patients' together. To the right, the sensitivity is given again for patients with 'early', 'moderate' and 'advanced' glaucoma separately. The specificity values for these three subgroups are by definition the same as for the entire glaucoma group, and are omitted to save space. In addition, the AUROC values are given for every parameter.

Table 7-2. Sensitivity, specificity and area under the ROC curve (AUROC) values for all GDx parameters

Table 7-3. Differences in AUROC values between various parameters in the 'all patients' group.

	DIFFERENCE IN AUROC VALUE AS COMPARED TO:	
	Maximum Modulation	**The Number**
Ellipse Standard Deviation (ESD)	0.018 (0.54)	-0.038 (0.0035)
Normalized Superior Area (NSA)	0.011 (0.65)	-0.043 (0.0016)
Normalized Inferior Area (NIA)	0.024 (0.35)	-0.030 (0.037)
Discriminant Analysis (DA)	0.055 (0.0059)	0.001 (0.91)

Presented are the AUROC values of the new parameters minus those of the maximum modulation (with p-values in parentheses) and the Number respectively. A positive sign indicates a better performance of the new parameters. With a negative sign, the existing parameters discriminated better. All data relate to the 'all patients' group.

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