Diagnostic accuracy of ganglion cell complex substructures in different stages of primary open-angle glaucoma

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ABSTRACT ●

Objective: To evaluate diagnostic accuracy of substructure of ganglion cell complex versus peripapillary nerve fiber layer (NFL) thickness using spectral domain optical coherence tomography (SD-OCT) in different stages of glaucoma.

Patients and Methods: Thirty eyes were normal, 120 were glaucomatous. Glaucomatous eyes were classified into: early glaucoma (46), moderate glaucoma (48), and severe glaucoma (26). Perimetry and SD-OCT were done. Peripapillary NFL thickness, ganglion cell layer (GCL), macular NFL thickness, combined GCL and macular ganglion cell complex (GCC), were recorded. Area under receiver operating characteristic curves (AUCs) was used to verify performance of different OCT parameters.

Results: Peripapillary NFL, GCL, and GCC thickness values were significantly different in all stages of glaucoma. All comparisons were significantly different; normal versus early, early versus moderate and moderate versus severe. The best parameters that distinguished normal from early stage were: peripapillary NFL (AUC: 0.90), GCC (AUC: 0.75), early from moderate stage were: peripapillary NFL thickness (AUC: 0.85), GCL (0.81),GCC (0.81), moderate from severe stage were: GCC (AUC:0.95), macular NFL (AUC:0.91), GCL (AUC:0.89), and peripapillary NFL (AUC:0.88).

Conclusions: Peripapllary NFL and GCC thinning showed paradoxical course. The most diagnosed parameter in early glaucoma was peripapillary NFL and in severe glaucoma was GCC. In severe glaucoma, macular NFL showed higher diagnostic power than GCL and peripapillary NFL. Ganglion cell complex mapping may provide good alternative to optic disc imaging in advanced glaucoma with poor fixation.

Primary open-angle glaucoma (POAG) is defined as chronic progressive optic neuropathy accompanied by characteristic cupping and atrophy of the optic disc, visual field loss, open angle, and no obvious systemic or ocular cause.[1] Standard perimetry cannot detect visual field defects until 20%–40% of ganglion cells have been lost.[2]

Staging glaucomatous damage into broad categories such as mild, moderate, and severe enhances management and promotes careful assessment of clinical damage, thereby facilitating monitoring for stability versus progression.[3] Measuring nerve fibre layer (NFL) thickness by optical coherence tomography (OCT) enables an objective and quantitative assessment of glaucomatous structural loss.[1] Peripapillary NFL thickness evaluation and optic nerve head (ONH) analysis had been considered for discriminating between different glaucoma stages with variable results.[4,5]

Ganglion cell complex (GCC) parameter was found to have significantly higher diagnostic power than total macular thickness parameters. It has been proven to be a useful method for glaucoma diagnosis and has potential for tracking glaucoma progression.[6,7]

Different studies showed the beneficial role of GCC analysis in glaucoma-suspect, ocular hypertensive, and POAG patients.[8,9] In addition, the clinical validity of GCC in advanced stages of glaucoma had been addressed[10]; however, little concern had been paid to the role of GCC individual substructure (nerve fibre layer, ganglion cell layer, and inner plexiform layer) in different stages of POAG. The aim of this study was to evaluate the diagnostic accuracy of GCC substructure versus peripapillary NFL thickness in different stages of POAG.

Patients and Methods

This was a nonrandomized, cross-sectional study. Eyes were considered glaucomatous if they had 2 consecutive abnormal visual field test results associated with ONH damage characteristic of glaucoma with or without elevated intraocular pressure ($\geq$21 mm Hg). Eyes were considered normal if they had intraocular pressure $<$21 mm Hg, normal optic disc appearance, and normal visual field. Normal visual field was defined as a mean defect and pattern standard deviation within 95% normal limits and a glaucoma hemifield test result within normal limits.

Patients who met the following criteria were excluded from the study: poor fixation, history of intraocular surgery, secondary glaucoma, systemic or ocular diseases, history of stroke, diseases that affect the macular area, and high myopia greater than $-$6 diopter.

All patients underwent measurement of best-corrected visual acuity, slit-lamp biomicroscopy, gonioscopy, Goldmann applanation tonometry, stereoscopic ophthalmoscopy of the optic disc, standard automated perimetry, and SD-OCT.

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Table 1—Baseline data of the study population

	Normal	Early	Moderate	Severe	F	*p*
Age	45.5 ± 13.32	43.2 ± 12.3	43.98 ± 14.52	50.12 ± 10.16	1.690	0.172
Spherical equivalent	−2.92 ± 0.64	−3.72 ± 1.31	−3.90 ± 1.11	−3.04 ± .84	2.532	0.065
VF MD (dB)	0.50 ± 0.10	−3.39 ± 1.88	−9.15 ± 1.69	−15.80 ± 3.00	161.036	<0.001*
IOP (mm Hg)	14.56 ± 0.53	14.1 ± 0.83	18.95 ± 0.83	22.40 ± 0.94	116.59	<0.001*

VF MD, visual field mean deviation; IOP, intraocular pressure.

*Significant $p < 0.05$.

Visual Field Testing

Visual field testing was done with Humphrey field analyzer (Carl Zeiss Meditec, Inc, Dublin, California, USA) using Swedish Interactive Thresholding Algorithm standard strategy, program 24-2. A visual field was considered abnormal if it showed the following criteria: ≥3 nonedge contiguous points demonstrating a threshold sensitivity loss ($p < 5\%$) with at least one of the points depressed at $p < 1\%$, or a >10-dB difference across nasal horizontal midline at 2 or more adjacent locations. In addition, abnormal glaucoma hemifield test was required.

The severity of glaucomatous damage was graded into early, moderate, and severe according to Hodapp, Parrish, and Anderson classification.[11]

Imaging with OCT

Optical coherence tomographic scanning was performed using Topcon 3D OCT-1000 mark II (Topcon, Tokyo, Japan). Data were obtained with the raster scanning technique (128 horizontal scans) centred on ONH covering a square area (6 mm × 6 mm × 1.7 mm). Total acquisition time was about 3.7 seconds.

Feripapillary NFL thickness maps and 3.4-mm-diameter circumpapillary OCT image can be generated from the 3D OCT data and can be manually or automatically repositioned to provide accurate centration around the ONH. Mean thickness of peripapillary NFL measurements outside 95% normal limits that were confirmed on 3 repeat scans were considered to be abnormal thinning.

ONH parameters included disc diameter, cup area and cup volume, cup-to-disc ratio horizontal and vertical, rim area, and rim volume.

The ganglion cell complex was measured using the scan protocol GCC. All patients had vertical cube scans of the macula (7 mm × 7 mm, 128 horizontal B-scans with 512 A-scans each) centred 1 mm temporal to the fovea. The area within 0.75 mm of the foveal centre was excluded because the GCC was too thin to be measured in that region.

Three thickness maps were generated by the machine for the macular scan:

1. Macular NFL: thickness measured from the internal limiting membrane (ILM) to posterior boundary of macular NFL.
2. Ganglion cell layer: GCC thickness measured from the posterior boundary of NFL to the posterior boundary of inner plexiform layer (IPL). This map represents both ganglion cell layer (GCL) and IPL because delineation of GCL alone is difficult.
3. GCC: thickness measured from ILM to outer IPL boundary. Therefore, this map represents macular NFL plus GCL and IPL (NFL + GCL + IPL)

Three corresponding probability (significance) maps were generated for the 3 thickness maps denoting areas of focal or generalized deviation from an age-, sex-, and race-matched database. In addition, average thickness of superior and inferior quadrants and total thickness were displayed for each map. Asymmetry maps comparing corresponding points in the superior and inferior hemifields were generated.

Statistical Analysis

Analysis was done using SPSS version 16. Mean values of peripapillary RNFL, GCL, macular NFL, and GCC thickness were compared between the normal and whole glaucoma group using the *t* test. Mean thickness in different stages was compared using 1-way analysis of variance followed by the Sidak post hoc test for multiple comparisons. Receiver operating characteristic (ROC) curves described the ability of each parameter to differentiate between different glaucoma stages by using area under the curve (AUC). An AUC of 1 (100% sensitivity and 100% specificity) represents a perfect test, whereas an AUC of 0.5 indicates a completely worthless test.

Results

A total of 150 eyes of 100 patients were enrolled in this study. Thirty eyes were normal; 120 were glaucomatous. Glaucomatous eyes were further classified into early glaucoma (46), moderate glaucoma (48), and severe glaucoma (26). There were 76 males and 24 females. Table 1 summarizes the baseline characteristics of the study population. No difference was detected between normal and glaucomatous eyes with regard to age and refractive error. A statistically significant difference of intraocular pressure and mean deviation was detected between the normal and glaucomatous eyes.

OCT measurements could discriminate all stages of glaucomatous damage. Peripapillary NFL measurement values were significantly different in all stages of glaucoma