Journal Of Medical Science And Clinical Research

IGM Publication   An Official Publication Of IGM Publication

Diagnostic utility of RNFL Thickness and Macular GCC Thickness in Primary Open Angle Glaucoma using Spectral Domain Optical Coherence Tomography in South Indian patients

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ABSTRACT
Purpose: *To evaluate and compare the diagnostic abilities of peripapillary retinal nerve fibre layer thickness (RNFL) parameters and macular Ganglion cell complex (GCC) parameters in the early detection of Glaucoma using high resolution spectral domain Optical Coherence Tomography(OCT).*
Materials and Methods: *Fifty eyes with Primary open angle glaucoma (POAG) and 50 normal eyes in the age group 35-70 years underwent Optical Coherence Tomographic evaluation. Statistical analysis was done using SPSS version11. Receiver operating characteristic curves (ROC) along with sensitivity at fixed specificity were studied for each tomographic parameter. Correlation of Tomographic data with visual field defects was evaluated by linear regression analysis.*
Results: *The visual field parameters of glaucoma patients showed a mean deviation value of (-6.1 ± 3.5) and pattern standard deviation value of (5.3 ± 3.3). Significant differences between glaucoma and normal subjects were found for all tomographic parameters. The best parameters based on Receiver operating characteristic curves and sensitivity at 95% specificity were RNFL-Average (AROC, 0.960; sensitivity, 80%) and GCC-Superotemporal quadrant (AROC, 0.912; sensitivity, 80%).*
Conclusions: *Both retinal nerve fibre layer thickness parameters and macular Ganglion cell complex parameters showed good diagnostic abilities in the diagnosis of early glaucoma using the spectral domain Optical Coherence Tomography. Better performance of macular parameters (compared to previous observations using older -Time Domain- Optical Coherence Tomography) were noted in the current study, however they did not outperform RNFL parameters.*
Keywords: *RNFL Thickness, GCC Thickness, SD OCT, Glaucoma.*

Introduction

Glaucoma is a multifactorial optic neuropathy characterized by loss of retinal ganglion cells (RGCs) and their respective axons, which compose the retinal nerve fiber layer (RNFL) [1]. Ganglion cells (RGCs) and retinal nerve fiber layer (RNFL)

constitute 30% to 35% of the macular retinal thickness. In addition, more than half the total number of ganglion cells (RGCs) in the retina are located in the central macula in more than one cell layer thickness [2,3]. Quantification of the changes that occur in the macula has hence been proposed to detect glaucoma in the early stages[3,4].

Currently, glaucoma is definitively diagnosed by the detection of visual field defects, which is a subjective test [5]. However, it has been shown that a 40% loss of RGCs occur before visual field (VF) defects manifest, and structural loss precedes detectable functional field loss by about 5 years [6]. Therefore, developing newer methods to quantify RGC-related glaucomatous changes is of utmost importance in the early detection of glaucoma.

The newer versions of Spectral-domain Optical Coherence Tomography (SD OCT) has enabled imaging of the retinal structure with a higher axial resolution (~five times), and a higher scan acquisition rate (60 times faster) than the conventional time domain OCT. This has specifically enhanced the measurement of the three main retinal layers associated with glaucomatous damage, namely retinal nerve fiber layer, ganglion cell layer and inner plexiform layer, collectively called the ganglion cell complex (GCC).

Previous studies using the time domain OCT have reported the peripapillary RNFL thickness parameters to have superior diagnostic ability than the macular thickness parameters in the diagnosis of early glaucoma [2]. However, many recent studies using the spectral domain (SD-OCT) have shown inconsistent results with better performance of macular parameters in a few of them [4,7] and equal performance [8,9,10] or even better performance of RNFL parameters [5,11] in others. There might also exist differences with respect to the staging of glaucoma and ethnicity of the study population. This study was designed to reassess and compare the diagnostic abilities of both RNFL and Ganglion cell complex parameters in the early detection of glaucoma using the spectral domain Cirrus HD OCT in a cohort of Primary open angle glaucoma patients from South India.

Materials and Methods

This cross sectional observational study was conducted at a tertiary eye hospital in South India between January 2013 and February 2014. The study design was approved by the Institutional Ethics Committee. Patients attending the Glaucoma clinic were screened for eligibility and were included in the study after obtaining informed consent. The cohort included 50 eyes (36 eyes of early stage and 14 eyes of moderate stage) of Primary open angle glaucoma (POAG) and 50 eyes of normal subjects in the age group 35-70 years. All methods in adherence to the tenets of the Declaration of Helsinki for research involving human subjects were observed in the study.

Early and moderate stage POAG patients were categorised based on the Hodapp-Anderson-Parrish classification [12] while the normal subjects were selected from healthy volunteers. Inclusion criteria were 1) best corrected visual acuity of 20/40 or better, 2) refractive error within ±5.0D sphere and ±2D cylinder, 3) reliable Standard automated perimetry (SAP) results and 4) willingness to participate in the study. Exclusion criteria were 1) presence of any media opacities that prevented good imaging, 2) intraocular surgery within the previous 6 months, 3) any retinal or neurological diseases other than glaucoma that could confound the results of visual field examination and structural measurements with the SDOCT.

All participants underwent a comprehensive ocular examination that included a detailed medical history, best corrected visual acuity measurement, slit-lamp biomicroscopy using 78D lens, Goldmann applanation tonometry, gonioscopy, dilated fundus examination, standard automated perimetry (SAP) using the Humphry field analyser and SD-OCT imaging with the Cirrus HD OCT.

POAG cases were identified based on the characteristic optic disc changes namely focal notching , diffuse neuro-retinal rim thinning, or retinal nerve fiber layer defects with corresponding visual field changes and open angles on gonioscopy. SAP was performed using the Humphrey Field analyzer model 750 (Zeiss Humphrey Systems, Dublin, CA, USA), with the Swedish interactive

threshold standard 30-2 algorithm. Reliability criteria were fixation losses less than 20% and false positive or false negative response rates less than 33%. Glaucomatous visual field defects were defined by any two of the following three Andersons criteria on SAP. 1) the presence of a cluster of three non-edge points on pattern deviation probability plot with a P-value of less than 5%, one of which having a P-value less than 1%, 2) a pattern standard deviation with a P-value less than 5%, or 3) a Glaucoma hemifield test result outside normal limits. Early and moderate stage glaucoma was determined according to the Hodapp Parrish Anderson criteria of mean deviation index.

The SD-OCT examination was performed with the Cirrus HD OCT 4000 (version 6.0) with the axial and transverse resolutions being 5μ and 15μ respectively. It uses a super-luminescent diode with a wavelength of 840 nm and a scan acquisition rate of 27,000 A-scans per second. Data for RNFL parameters were acquired using the Optic Disc Cube 200 × 200 scan protocol and calculated by layer seeking algorithms for the entire cube. A total of 256 specific A-scans aligned in a circle of 3.46 mm diameter centred on the optic disc are performed to provide the RNFL parameters. They include average RNFL thickness and sectoral RNFL thickness in clock hours and quadrants namely superior, inferior, nasal and temporal.

The Ganglion cell complex (GCC) maps were based on the macular scanning protocol 512 × 128 centred on the fovea. The ganglion cell analysis (GCA) algorithm was used to identify the outer boundary of the RNFL and the inner plexiform layer (IPL) so that the distance between the RNFL and the IPL outer boundary segmentations yields the combined thickness of the ganglion cell complex (GCC) and IPL. The average, and sectoral (superior, superonasal, inferonasal, inferior, inferotemporal, and superotemporal) GCC thickness parameters were analyzed. A single well trained operator was assigned to perform the scans under pupil dilatation. Only good quality OCT scans with signal strength more than 6 were included for the analysis.

Statistical analysis was done using SPSS version11. Receiver operating characteristic curves (ROC) along with sensitivity at fixed specificity were studied for each tomographic parameter. Correlation of Tomographic data with visual field defects (Mean deviation) was evaluated by linear regression analysis.

Results

A total number of 50 eyes of 41 cases of Primary open angle glaucoma and 50 eyes of 36 normal subjects were recruited for the study and analysed. The mean age among the cases was (52.41 ± 7.4) years and that of normal subjects was (50.1 ± 8.0) years (p=0.139). No statistical significance was noted with respect to gender among the two groups. The visual field parameters of glaucoma patients showed a mean deviation (MD) value of (-6.1 ± 3.5) and pattern standard deviation (PSD) value of (5.3 ± 3.3). The mean values of the RNFL parameters, the ROC and the sensitivity at fixed specificity values of the parameters are shown in Table 1 .

Significant differences were found for all the RNFL parameters (p<0.001) in glaucoma eyes compared to normal subjects. The ROC for RNFL parameters ranged from 0.720 (95% CI 0.618-0.822) for the nasal quadrant to 0.960 (95% CI 0.929-0.992) for the RNFL AV parameter. RNFL AV appeared to be the best RNFL parameter taking into consideration both the ROC value and sensitivity at fixed specificity (80% sensitivity at 95% fixed specificity). The mean values of the GCC parameters, the ROC values and the sensitivity at fixed specificity of the parameters are shown in Table 2 .The GCC parameters showed significant differences (p < 0.001) compared to normal subjects. The ROC for the GCC parameters ranged from the lowest of 0.734 (95% CI 0.635-0.833) for the inferonasal quadrant to 0.915 (95% CI 0.864-.965) for the inferotemporal quadrant. However the GCC ST (superotemporal quadrant) appeared to be the best GCC parameter considering the higher values for both ROC (0.912) and 80% sensitivity at fixed specificity of 95%. The GCC AV was also found to have high ROC value of 0.906 (95% CI 0.849-0.962) with 70% sensitivity at 95% specificity. The ROC of RNFL AV (0.960) was higher compared with GCC AV (ROC value 0.906) and this was

statistically significant (p<0.001) (Figure.1). The relationship between MD and the SD OCT parameters showed significant correlations between both RNFL AV (r = - 0.750, p<0.001) and GCC AV parameters (r = - 0.589, p<0.001) on linear regression analysis. The correlation was found to be higher for the RNFL AV parameter.

Table 1: RNFL thickness parameters in glaucoma and healthy eyes with ROC and sensitivities at fixed specificities

RNFL thickness (microns)	Normal subjects (Mean±SD)	Early glaucoma (Mean±SD)	P value	ROC	95% CI	Sensitivity at 95% specificity	Sensitivity at 80% specificity
RNFLS	119.6±12.3	89.3±19.9	0.001	0.917	0.861-0.973	78%	84%
RNFLI	122.8±17.3	90.3±20.9	0.001	0.895	0.833-0.957	58%	86%
RNFLN	69.8±9.4	62.3±10.3	0.001	0.720	0.618-0.822	40%	64%
RNFLT	63.4±7.2	53.4±10.8	0.001	0.822	0.737-0.906	35%	70%
RNFLAV	94.2±7.8	73.7±10.1	0.001	0.960	0.929-0.992	80%	92%

Table 2: GCC parameters in glaucoma and healthy eyes with ROC and sensitivities at fixed specificities

| GCC thickness (microns)	Normal subjects (Mean±SD)	Early glaucoma (Mean ± SD)	P-value	ROC	95% CI	Sensitivity at 95% specificity	Sensitivity at 80% specificity
GCCS	82.9±5.6	72.5±8.06	0.001	0.871	0.800-0.942	66%	76%
GCCI	80.1±6.5	69.8±10.5	0.001	0.814	0.732-0.895	68%	75%
GCCSN	84.2±6.5	78.2±6.9	0.001	0.745	0.640-0.842	28%	53%
GCCIN	81.9±6.5	75.7±7.6	0.001	0.734	0.635-0.833	72%	75%
GCCIT	81.8±5.5	68.8±9.9	0.001	0.915	0.864-.965	66%	78%
GCCST	80.7±5.1	70.6±6.2	0.001	0.912	0.853-0.971	80%	86%
GCCAV	107.8±23.5	72.5±5.5	0.001	0.906	0.849-0.962	70%	82%
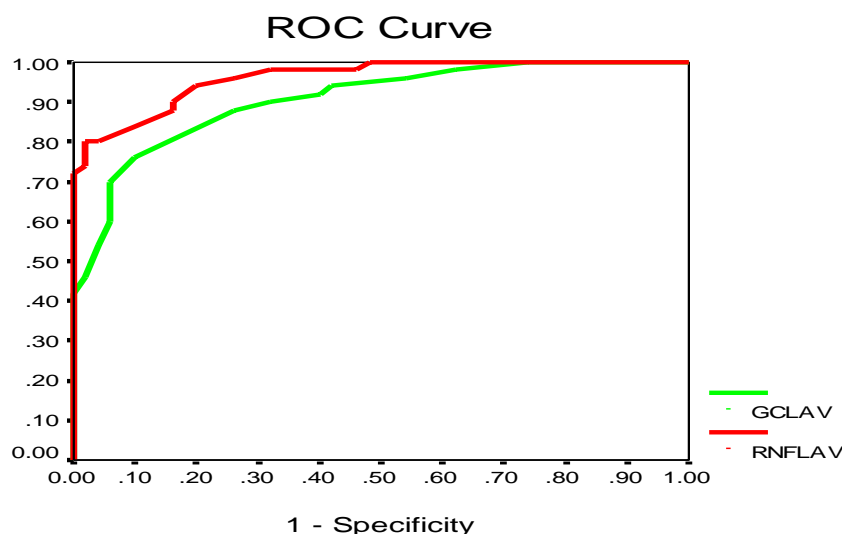
Figure 1: ROC graph of RNFL AV and GCC AV parameters

Discussion

This study reassessed and compared the diagnostic abilities of RNFL and GCC parameters in early detection of glaucoma using spectral domain Cirrus HD OCT in a cohort of Primary open angle glaucoma patients from South India.

Both RNFL and GCC parameters were found to have good diagnostic abilities. However in our study, RNFL parameters showed statistically significant higher performance compared to the GCC parameters. The results are in agreement with few studies notably the study by Fang Yuan et al [5] in early POAG and Lisboa R et al[11] in preperimetric glaucoma which also showed improved diagnostic abilities of both parameters, however with better performance of RNFL AV over macular parameters using Fourier domain OCT. In other studies, HL Rao et al, [4] in early POAG eyes and Seong et al, [13] in normal tension glaucoma eyes with early visual field damage, found comparable diagnostic abilities between average RNFL and macular parameters using the Fourier domain RTVue OCT. In few studies, Mori et al [14], HL Rao et al[4] reported selective measurements of macula inner retinal (MIR) volume by Fourier domain OCT to have better diagnostic performance among macular parameters in early diagnosis of glaucoma.

The inconsistencies in the diagnostic capabilities of macular parameters in various studies using SD OCT may be due to the fact that SD OCT can measure the GCC thickness in the centre of macular area (7×6 mm2) only, thus excluding the glaucomatous damage outside this region which might be affected in early glaucoma. Also, there may be differences in the study groups based on the staging of glaucoma as well as ethnicity of the study population.

Our study with SD OCT shows that although the performance of macular parameters improved compared to stratus OCT (thus corroborating with Zeimer's hypothesis) [3], they did not outperform RNFL parameters in the diagnostic ability to detect early glaucoma [15]. This necessitates development of better OCT scanning techniques and segmentation algorithms to provide more accurate macular measurements.

Conclusions

Both RNFL and macular GCC parameters showed good diagnostic abilities in the early detection of glaucoma using Spectral Domain OCT. Though the macular (GCC) parameters showed improvement in performance (compared to older -Time Domain- Optical Coherence Tomography), they did not outperform the RNFL parameters in the current study.

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