

A COMPARATIVE STUDY OF RETINAL NERVE FIBER LAYER THICKNESS IN NORMAL AND GLAUCOMATOUS EYES USING SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY

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ABSTRACT

BACKGROUND

Glaucoma is the leading cause of irreversible blindness in the world. The peripapillary Retinal Nerve Fiber Layer (RNFL) thickness evaluation is a useful method to detect the early structural damage of glaucoma. The purpose of present study is to assess and compare the Retinal Nerve Fiber Layer thickness in Primary Open Angle Glaucoma and control group using SD-OCT.

MATERIALS AND METHODS

70 eyes with POAG and 70 normal eyes were included in the study. All subjects underwent basic workup for glaucoma including standard automated perimetry and optic nerve head evaluation using Cirrus SD-OCT.

RESULTS

Average RNFL thickness is significantly reduced in diagnosed cases compared to normal subjects. In POAG cases it is $58.19 \pm 15.87 \mu\text{m}$ and in normal subjects it is $91.91 \pm 6.85 \mu\text{m}$ ($p < 0.001$). There is positive correlation between MD and average RNFL thickness and negative correlation between PSD and RNFL thickness. CD ratio has a negative correlation with RNFL thickness.

CONCLUSION

The result indicates that SD-OCT helps largely to detect and measure decrease in RNFL thickness in diagnosed glaucoma cases. So it is noteworthy in diagnosing glaucoma at an early stage consequently preventing further damage.

KEYWORDS

Retinal Nerve Fiber Layer, Primary Open Angle Glaucoma, Standard Automated Perimetry, Spectral Domain Optical Coherence Tomography.

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BACKGROUND

Glaucoma is the leading cause of irreversible blindness in the world. POAG is recognized as chronic, progressive optic neuropathy that is associated with characteristic cupping and atrophy of the optic disc, visual field (VF) loss and open angles.¹ By appropriate screening and treatment, glaucoma usually can be identified, and its progress arrested before significant effects on vision occurs. Worldwide prevalence of glaucoma is 3.54%. The number of people with glaucoma across the globe was estimated to be 64.3 million in 2013 which will increase to 76.0 million in 2020 and 111.8 million in 2040 among the age group of 40 to 80 years. The prevalence of POAG is highest in Africa and the prevalence of PACG is highest in Asia.² As per the data from World Health Organization, India has a 1% prevalence of blindness. There are about 8.9 million blind in India and 12.8% are due to glaucoma. Vellore Eye Survey (VES) is the

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first comprehensive study of the prevalence for eye diseases including glaucoma, of an Indian population.

Recent population-based studies in southern India have reported various prevalence rates of primary open-angle glaucoma (POAG). The Vellore Eye Survey (VES) reported a prevalence of 0.41% for POAG in the 30 to 60 year age group whereas the Andhra Pradesh Eye Diseases Study (APEDS) estimated the prevalence of POAG in the urban population to be 2.56% in those aged 40 years and older. The prevalence of POAG in the Aravind Comprehensive Eye Survey (ACES) was 1.2%.^{3,4,5,6} On the basis of the available data, it is estimated that there are approximately 11.2 million persons aged 40 years and older with glaucoma in India. Primary open angle glaucoma is estimated to affect 6.48 million persons.⁷ Projected changes in world population will continue to increase the number and proportion of older people.⁸

Glaucomatous optic neuropathy causes progressive death of retinal ganglion cells and their axons. These structural changes precede visual field defects as measured by standard automated perimetry. Clinically, visual field loss often correlates with nerve fiber layer loss and optic nerve damage. It is well established that significant amount of ganglion cell death (40%) occurs before any visual field defect is produced.^{9,10,11,12} Early detection of glaucoma has focused on evaluation of the ONH and the RNFL, because



both the RNFL and the ONH can be imaged and have been shown to undergo structural changes prior to clinically detectable visual field loss. Nerve fiber layer thinning is seen in glaucoma, because it is directly correlated with loss of ganglion cells, which is assumed to be a primary event in glaucomatous damage. Since RNFL thinning and ONH changes are irreversible, early diagnosis is essential.¹³ Optical Coherence Tomography (OCT) has emerged as an important tool in ocular imaging.¹⁴ Careful evaluation of the optic nerve head and RNFL is crucial in diagnosis of glaucoma. It also provides information about the location and severity of visual field damage. All currently available OCT devices provide color-coded deviation, thickness, and significance maps that aid the clinician in determining whether the scanning results are within normal or outside normal range.

Aims and Objectives

To quantitatively assess and compare the thickness of retinal nerve fiber layer in normal and eyes with POAG using SD-OCT.

MATERIALS AND METHODS

All the patients attending the Out-Patient Department of Upgraded Department of Ophthalmology in NSCB Medical College Hospital-Jabalpur in the duration March 2015 – April 2016 were evaluated and 70 eyes with POAG and 70 normal age matched control were included in the study.

Study Design

Case control study.

Sample Size

The mean difference in Retinal Nerve Fiber Layer (RNFL) thickness was considered 42 ± 12 that is, 30-54 (with absolute precision 12) for sample size calculation 16. At 5% marginal error, 95% confidence limit and 80% power the minimum required sample will be 65. Therefore we have taken a required adequate sample size of 70 primary open angle glaucoma and 70 normal eyes as 1:1 ratio design. The formula of simple random sampling was used for sample size estimation.

$$n = z^2pq / l^2$$

where –

n = sample size

z = 1.96 (at 5% alpha, 95% confidence limit and 80% Power)

p = 0.42

q = 1 – p

l = 0.12

Informed consent was obtained from all subjects. The tenets of declaration of Helsinki were followed. All patients were subjected to detailed history taking regarding following points-

- a) Relevant history: diminution of vision, pain, redness, watering, photophobia, coloured halos, headache, vomiting.

- b) History of surgery: example cataract surgery, filtering surgery, posterior segment surgery.
- c) History of associated systemic illness like diabetes mellitus, hypertension, bleeding disorders or any other.
- d) History of trauma.
- e) Family history.
- f) Personal history.

All patients underwent a detailed clinical evaluation.

Ocular Examinations

1. Snellen's visual acuity testing.
2. Refraction.
3. Evaluation of intraocular pressure.
4. Slit lamp biomicroscopy of anterior segment.
5. Gonioscopy.
6. Dilated Fundus examination by direct ophthalmoscopy and 90D examination.
7. Automated Perimetry by Humphrey field analyser.
8. Carl Zeiss Spectral Domain Optical Coherence Tomography.

All subjects underwent Automated Perimetry on the Humphrey's Field Analyser using the 30-2 testing protocol by SITA strategy. Fixation losses of more than 20% and false-positive and false-negative rates of more than 33% were excluded. We used two of VF global indices, Mean Deviation (MD) and Pattern Standard Deviation (PSD) in this study.

Inclusion Criteria

All patients diagnosed as POAG as per below mentioned criteria and normal age matched controls were included in the study.

POAG Patients Diagnosed if Below Criteria Are Met-

- a) Elevated intraocular pressure (IOP) (greater than 21mm Hg) without treatment on at least two separate visits.
- b) Glaucomatous optic disc appearance.
- c) Glaucomatous VF damage.
- d) Wide and open angle on gonioscopy.
- e) No other obvious causes for these changes.

Control Subjects Were Included if They Had

- a) IOP measurements less than 21mm Hg on at least two separate occasions.
- b) Absence of glaucomatous optic nerve head changes, and no asymmetry in cup disc ratio between two eyes.
- c) A normal visual field.
- d) No family history of glaucoma.
- e) Normal fundus examination with no evidence of optic disc or macular disease like drusen, optic disc pallor, optic disc haemorrhage, age-related macular degeneration, or diabetic retinopathy.

Exclusion Criteria

- a) Age less than 18 years.

- b) Chorioretinal degeneration, macular degenerations or maculopathies.
- c) History of trauma.
- d) Arteritic ischemic optic neuropathy.
- e) Optic Neuropathies and optic neuritis.
- f) Unreliable and uncooperative patients for OCT and perimetry.
- g) Secondary glaucoma.
- h) OCT Image with signal strength of <4/10 was excluded.

Statistical Methods

Data was double key entered in Microsoft Excel 2003 worksheet. All the illogical entries and inconsistencies were resolved by data editing. Non numeric data were coded numerically before the analysis. Categorical variables were summarized in frequency and percent distribution. Continuous variables were summarized in Mean (± SD). Normal distribution of continuous variable was checked and if data found skewed, then data was log transformed to normalized before analysis otherwise non parametric tests were applied. Test of difference between two means, student t test was applied. Correlation matrix was used to test the presence or absence of association between two distributions. Statistical significance was considered at alpha

0.05. Receiver Operating Characteristic (ROC) curves were used to describe the accuracy of OCT retinal nerve fiber layer parameter to differentiate glaucoma from normal control.

All the statistical analysis was performed using STATA 12.0, College Station, TX-USA.

OCT Technique

Subjects were scanned with the Stratus OCT (model 4000, software.2.0). Scan protocol of Cirrus HD-OCT called 'optic disc cube 200 x 200' is used for measurement of RNFL thickness.

RESULTS

Seventy eyes of thirty five POAG patients (20 male and 15 female with mean age 61.09 ± 8.15) and seventy eyes of thirty five normal age matched control (19 male and 16 female with mean age 55.46 ± 8.51) were included in this study. The average RNFL thickness was significantly decreased in POAG patients as compared to control (58.14 ± 15.76 in POAG patients and 91.91 ± 6.85 in control group).

The RNFL thickness was significantly decreased in inferior, superior, nasal and temporal quadrant in POAG patients. (p<0.001).

	Control	POAG
Age (Years) (Mean ± SD)	55.46 ± 8.51	61.09 ± 8.15
Gender (Male/Female)	19/16	20/15
No. of Eyes	70	70
IOP(mm of Hg)	14.82 ± 1.72	24.49 ± 1.91
Average RNFL thickness (in µm)	91.91 ± 6.85	58.14 ± 15.76
Average CD Ratio	0.38 ± 0.06	0.75 ± 0.09
MD (in decibel)	-1.71 ± 0.87	-9.07 ± 6.23
PSD (in decibel)	1.84 ± 0.30	6.34 ± 3.36

Table 1. The Demographic Data, IOP, Average RNFL Thickness, Average CD Ratio MD and PSD

RNFL Thickness (in µm)	Control	POAG	Significance
Inferior RNFL	120.79 ± 10.53	64.83 ± 26.56	t=16.38 p<0.0001
Superior RNFL	112.36 ± 11.37	73.40 ± 29.04	t=10.45 p<0.0001
Nasal RNFL	71.39 ± 7.97	49.07 ± 14.54	t=11.26 p<0.001
Temporal RNFL	62.90 ± 08.10	47.03 ± 12.47	t=8.93 p<0.001

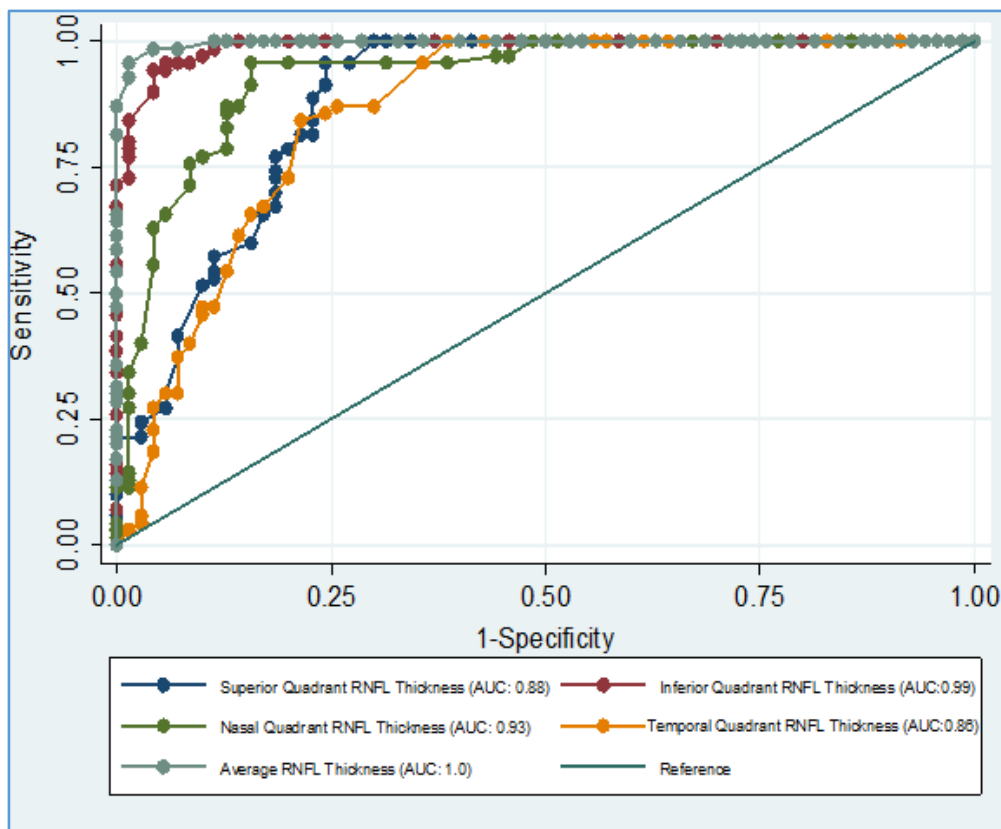
Table 2. Comparison of RNFL thickness in four quadrants among POAG and control group

In diagnosed POAG patients, the Average RNFL is inversely related to PSD and Average CD Ratio with a high significance. (p<0.0001, r= -0.45 for PSD, p=0.05, r= -0.23 for Average CDR). Conversely Average RNFL is directly related to MD (p<0.0001).

Group	MD	PSD	Average CD Ratio
Average RNFL thickness in control	0.03 p=0.75	-0.04 p=0.74	-0.05 p=0.62
Average RNFL thickness in POAG	0.57 p<0.0001	-0.45 p<0.0001	-0.23 p=0.05

Table 3. Correlation of Average RNFL thickness with different parameters among POAG and control group

The Area under curve (AUC) in Receiver Operating Characteristic analysis (ROC) was highest for average RNFL thickness (AUC=1.00) followed by inferior quadrant RNFL thickness (AUC=0.99). Thus the best parameter to differentiate among POAG cases from control cases was average RNFL thickness.



Graph 1. Area under ROC Curve of Different Quadrant and Average RNFL Thickness

DISCUSSION

The primary aim to treat glaucoma is the early diagnosis. Visual field is important in diagnosis but it cannot detect loss until 20%-40% ganglion cell layer has been lost. Nevertheless it is essential tool to diagnose and measure the progression. Ganglion cell layer and RNFL can be measured accurately using OCT, and its importance has already been established in diagnosis of glaucoma and other diseases.

In our study, we found that normal eyes have highest RNFL thickness in inferior quadrant followed by superior, nasal and temporal quadrants. Similar results were found in study by Bowd et al. They concluded that normal eyes have a double hump shaped RNFL thickness curve with peaks at superior and inferior quadrants and troughs at nasal and inferior quadrants and found significant thinning of RNFL in glaucomatous eyes.¹⁵

Subbiah S et al.¹⁶ while analysing the results, glaucoma patients, glaucoma suspects and of normal subjects using OCT found that RNFL thickness was greatest in superior and inferior quadrant in normal subjects. The RNFL was thinner in glaucomatous eyes in the inferior, superior, nasal and temporal quadrants when compared to normal ($p < 0.001$).

Study by Vandana B et al.¹⁷ analysed glaucoma patients and normal subjects and observed that the mean RNFL thickness in corresponding advanced and early glaucomatous eyes were significantly lower than in normal control subjects ($p < 0.0001$). A linear correlation was found between RNFL thickness and MD in the early and advanced glaucomatous eyes and concluded that measurement of RNFL thickness is useful for detection of early nerve fiber loss owing to glaucoma. The results are comparable with the

present study which also shows a statistically significant decrease in average RNFL thickness in glaucomatous eyes as compared to control ($p < 0.001$) and a positive correlation in MD and average RNFL ($r = 0.58$; $p < 0.001$). Sihota et al.¹⁸ while evaluating role of OCT in differentiating normal and glaucomatous eyes found a statistically significant difference in all RNFL thickness parameters ($p < 0.001$). Average RNFL thickness was found to have highest area under ROC curve among various parameters. In present study area under ROC curve among different RNFL thickness parameters was found to be highest for average RNFL thickness (AUC=1.00) followed by inferior quadrant RNFL thickness (AUC = 0.99). Thus the best RNFL parameters for differentiation of glaucomatous eyes from normal eyes were average and inferior quadrant RNFL thickness.

Leite et al.,¹⁹ also reported that the RNFL thickness parameter with the largest capability of distinguishing normal eyes from glaucomatous eyes was the global RNFL thickness for the Cirrus (AUC 0.88).

CONCLUSION

- OCT is capable of detecting changes at the level of Retinal Nerve Fiber Layer in Glaucomatous eyes.
- OCT has shown to obtain accurate and reproducible Retinal Nerve Fiber Layer measurements which can not only help in early detection of glaucoma but also in assessment of its progression.
- Thus OCT can serve as a useful tool in diagnosis, management, prognostication and research in Glaucoma.

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