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Original Article

Ophthalmology Section

Ability of Optical Coherence Tomography in Early Detection of Primary Open Angle Glaucoma

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ABSTRACT

Introduction: As glaucoma is one of the leading causes of blindness, its early diagnosis is crucial. Standard Visual Field (VF) examinations are used in the diagnosis and follow-up of glaucoma, but the major drawback is that the abnormalities do not appear until 20-40% of ganglion cells are lost. Defects in the Retinal Nerve Fiber Layer (RNFL), measured by Optical Coherence Tomography (OCT), is an excellent objective and quantitative method in the diagnosis and management of glaucoma at earlier stages.

Aim: To assess the ability of OCT in diagnosing early glaucomatous changes using RNFL, Optic Nerve Head (ONH) and macular thickness parameters.

Materials and Methods: A hospital-based case control study was done for 18 months at Department of Ophthalmology, Sawai Man Singh (SMS) Hospital and Medical College, Jaipur, Rajasthan, India. Fifty patients meeting the inclusion criteria were evaluated in the study as case group. To compare the results with those of a normal population 50 age and sex matched subjects were included. Each subject underwent detailed ocular examination and RNFL, ONH and macular thickness parameters were measured using Spectral Domain (SD) OCT. The unpaired t-test was used to compare continuous variables and Chi-square test was used to compare categorical variables. The Area Under the Curve (AUC) with its 95% Confidence Interval (CI) was calculated. The p-value <0.05 was considered significant.

Results: A total of 50 glaucoma or glaucoma suspect cases and 50 controls partcipated in the present study, i.e., 100 eyes in each group were studied. Mean RNFL thickness, superior thickness, inferior thickness and temporal thickness were significantly ($p<0.05$) lower among cases than controls. Cup area, cup/disc (C/D) area ratio, horizontal and vertical cup to disc ratio (CDR) were significantly ($p=0.0001$) higher among cases than controls. Vertically Integrated Rim Area (VIRA) was significantly ($p<0.05$) lower among cases (0.19±0.13) than controls (0.28±0.05). There was no significant ($p>0.05$) difference in disc area between cases and controls. All the macular thickness parameters were significantly ($p<0.05$) lower among cases than controls except fovea. Overall, ONH and macular thickness parameters had high sensitivity and specificity than RNFL parameters in glaucoma patients.

Conclusion: The present study found that a combination of RNFL, ONH and macular thickness parameters improved the diagnostic accuracy of OCT in early detection of Primary Open Angle Glaucoma (POAG).

Keywords: Macular thickness, Optic nerve head, Retinal nerve fibre layer, Vertically integrated rim area

INTRODUCTION

Glaucoma is one of the leading causes of blindness all over the world and reduces the RNFL thickness imaged with OCT [1,2]. Globally, glaucoma is the second most common cause of blindness after cataract. In India, glaucoma accounts for 12% of blindness and 11.4% of low vision. The prevention and treatment of glaucoma is complicated by the lack of early warnings for impending vision loss and uncertainties in the diagnosis as Primary Open Angle Glaucoma (POAG) is asymptomatic in its early stages [3].

POAG is characterised by optic neuropathy of multifactor origin with a characteristic acquired atrophy of the ONH and progressive structural loss of Retinal Ganglion Cells (RGC) and their axons developing in the presence of open anterior chamber angles, and manifests characteristic VF abnormalities, that eventually may result in vision loss and irreversible blindness [4].

Detection of structural loss plays a fundamental role in diagnosing the disease as well as management of glaucoma. While structural damage in glaucoma can be assessed subjectively by clinically examining the ONH and peripapillary RNFL, the introduction of ocular imaging modalities into clinical management has made objective and quantitative evaluation of ocular structures easier.

The OCT, first described in 1991, is a noncontact, noninvasive imaging technique that can reveal layers of the retina by looking at the interference patterns of reflected laser light [5]. It is an innovative diagnostic tool in tomographic imaging of tissues. In the field of ophthalmology, its ease of access to different areas in the eye allows its use as an excellent diagnostic technology [6].

Early diagnosis of glaucoma is crucial and plays an important role in early prevention of the disease as it is the second leading cause of blindness. Standard VF examinations are used in the diagnosis and follow-up of glaucoma, but one of its drawbacks is that the abnormalities do not appear until 20-40% of ganglion cells are lost [7]. Earlier defects in the RNFL measured by OCT provide an excellent objective as well as quantitative method in the diagnosis and management of glaucoma [8]. The principle of low coherence interferometry used in OCT in recording the echo time delay and intensity of backscattered light from various retinal layers allow it to measure an accurate thickness of the RNFL [9].

The commercially available iteration of the OCT technology, spectral domain SD-OCT, has theoretical advantages over the earlier generation of Time Domain TD-OCT in terms of higher axial resolution power and faster speed of scanning that lead to lower susceptibility to artefacts caused by the movements of the eye. It is suggested that SD-OCT offers improved reproducibility; however, its capacity to diagnose glaucoma is statistically similar [10]. The present study was a comparative type of cross-sectional study for early detection of glaucoma using OCT.

MATERIALS AND METHODS

A hospital-based case control study was conducted with the approval of the Institutional Ethics Committee (No.-846/MC/EC/2019) and as per the tenets of the Declaration of Helsinki at Upgraded Department of Ophthalmology, SMS Hospital and Medical College, Jaipur, India. The study was conducted for 18 months, data collection was done from July 2018 to July 2019 and another six months from August 2019 to January 2020 were taken for data and statistical analysis.

All subjects were fully informed about the nature of the study according to the codes of ethics in the Declaration of Helsinki protocol, and then written consent for participation was obtained from all the participants.

Sample size calculation: Sample size was calculated at 80% study power and α error at 0.05 assuming SD at 0.34 mm^2 for VIRA as per results of seed article [11]. For minimum detectable mean difference at 20 mm^2 in VIRA, 45 participants in each of the two groups were required. It has been enhanced and rounded off to 50 patients as final sample size expecting 10% attrition. A total of 50 patients meeting the inclusion criteria were evaluated in the study as a case group. To compare the results with those of a normal population, 50 age and sex matched controls either from the hospital staff or patient's attendant were included.

Inclusion criteria: Glaucoma/glaucoma suspect subjects: subjects with Intraocular Pressure (IOP) ≥21 (two consecutive readings); Open anterior chamber angle on gonioscopy; glaucomatous ONH and VF changes may be present (glaucoma subjects) or may not be present (glaucoma suspects) were included as case group in the study. Healthy subjects: Subjects with IOP ≤21 with no history of raised IOP, best corrected visual acuity more than 6/12 were included as healthy control group.

Exclusion criteria: Patients having Primary Angle-Closure Glaucoma (PACG), non-glaucomatous optic neuropathy, any associated retinal disease and having uveitis were excluded from the study.

Study Procedure

Each subject underwent detailed ocular examination including best corrected visual acuity, slit lamp examination, intra-ocular pressure measurement using Goldmann's Applanation Tonometer (IOPGAT) and gonioscopy using three mirror gonioscopy lens and and the angle was graded using Shaffer classification [4]. The VF analysis was done by Humphrey field analyser. RNFL, ONH and macular thickness parameters were measured using SD OCT (TOPCON 3D OCT) after pharmacological dilatation of the pupil with tropicamide 0.8% and phenylephrine 5%. The RNFL thickness parameters were measured at superior, inferior, nasal, temporal, 1 to 12 o'clock positions. The ONH parameters included in the study were disc area, cup area, C/D area ratio, rim area, horizontal CDR, vertical CDR and VIRA.

For macular thickness assessment 3D radial module was used; in this module according to Early treatment diabetic retinopathy study, macula was divided into nine regions with three concentric rings; the nine regions are superior outer, inferior, outer, temporal, outer nasal outer, superior and inferior inner, temporal and nasal inner and the fovea. Thickness of macula was measured at these all regions.

STATISTICAL ANALYSIS

The results were presented in frequencies, percentages and mean±SD. The unpaired t-test was used to compare continuous variables and chi-square test was used to compare categorical variables. The Receiving Operating Curve (ROC) analysis was carried out. The AUC with its 95% CI was calculated. The sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) with its 95% CI was calculated. The p-value <0.05 was considered statistically significant. All the analysis was carried out on Statistical Package for the Social Sciences (SPSS) version 16.0 (Chicago, Inc., USA).

RESULTS

A total of 50 glaucoma/glaucoma suspect cases and 50 controls were included in the study, i.e., 100 eyes in each group. The mean age of cases and controls was 59.26±9.90 and 59.40±10.58 years respectively. [Table/Fig-1] showing comparability of the groups in terms of age.

Variables	Cases (n=50)	Controls (n=50)	p-value
Age (in years)	59.26±9.90	59.40±10.58	0.94
Gender			
Male (n, %)	31 (62)	35 (70)	0.39
Female (n, %)	19 (38)	15 (30)	
IOPGAT (Mean±SD)	22.88±3.68	15.88±1.78	0.001*
Gonioscopy			
Grade 3 (n, %),	13 (26)	11 (22)	0.87
Grade 3-4 (n, %)	20 (40)	20 (40)	
Grade 4 (n, %)	17 (34)	19 (38)	

[Table/Fig-1]: Distribution of age, gender between the groups; Comparison of IOP GAT and gonioscopy between the groups.
Chi-square test, SD: Standard deviation; IOP: Intra ocular pressure; GAT: Goldmann's applanation tonometer. [1]Unpaired t-test, *p-value <0.05 was considered statistically significant

More than half of patients of both cases (62%) and controls (70%) were males. There was no significant (p>0.05) difference in gender between the groups showing comparability of the groups in terms of gender [Table/Fig-1]. IOPGAT was significantly (p=0.001) higher among cases (22.88±3.68) compared to controls (15.88±1.78) [Table/Fig-1].

In gonioscopy measurement, grade 3-4 was among more than one third of patients in both cases and controls each constituted 40%. There was no significant (p>0.05) difference in gonioscopy between the groups [Table/Fig-1].

[Table/Fig-2] shows the comparison of VFs between the groups. There was significant (p=0.001) difference in VFs between the groups.

Average thickness, superior thickness, inferior thickness and temporal thickness were significantly (p=0.0001) lower among cases than controls. Thickness was also lower among cases than controls at all the time periods [Table/Fig-3,4].

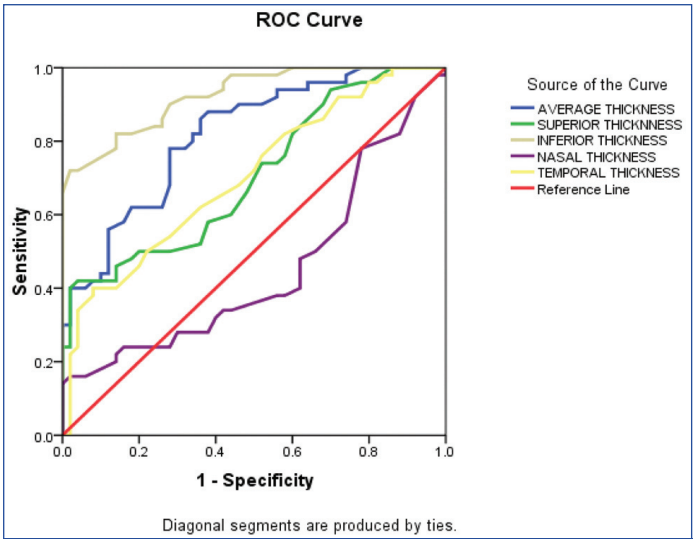
Groups	VF-MD (dB) (Mean±SD)
Cases	-8.84±5.15
Controls	-1.51±0.21
p-value[1]	0.001*

[Table/Fig-2]: Comparison of Visual Fields (VF)- MD (dB) between the groups.
VF: Visual fields; MD: Mean deviation; dB: Decibels; SD: Standard deviation, [1]Unpaired t-test, *p-value <0.05 was considered statistically significant

OCT-RNFL thickness (in microns) parameters	Cases (n=50)	Controls (n=50)	p-value[1]
Average thickness	81.93±11.87	93.65±6.20	0.0001*
Superior thickness	101.06±17.21	113.94±9.54	0.0001*
Inferior thickness	92.44±16.67	117.20±9.87	0.0001*
Nasal thickness	68.60±11.75	68.70±8.48	0.96
Temporal thickness	65.74±12.37	74.78±9.78	0.0001*
Thickness at 1 O'clock	90.78±19.47	111.52±12.08	0.0001*
Thickness at 2 O'clock	69.42±13.71	91.64±13.45	0.0001*
Thickness at 3 O'clock	55.64±10.86	68.24±12.11	0.0001*
Thickness at 4 O'clock	59.96±10.59	76.82±11.34	0.0001*
Thickness at 5 O'clock	84.78±15.96	103.30±17.51	0.0001*
Thickness at 6 O'clock	93.04±17.88	124.66±10.94	0.0001*
Thickness at 7 O'clock	90.40±20.86	121.46±10.13	0.0001*

Thickness at 8 O'clock	66.44±10.39	71.64±8.59	0.008*
Thickness at 9 O'clock	56.58±8.03	56.92±6.98	0.82
Thickness at 10 O'clock	69.58±13.94	79.54±12.41	0.0001*
Thickness at 11 O'clock	95.98±19.05	116.20±12.32	0.0001*
Thickness at 12 O'clock	92.50±19.21	113.88±11.03	0.0001*

[Table/Fig-3]: Comparison of OCT-RNFL thickness (in microns) parameters between the groups.
OCT: Optical coherence tomography; RNFL: Retinal nerve fiber layer, [1]Unpaired t-test, *p-value <0.05 was considered statistically significant



[Table/Fig-4]: ROC curve showing sensitivity and specificity of OCT-RNFL thickness (in microns) parameters in differentiating between early glaucomatous and healthy eyes.
ROC: Receiving operating curve

Cup area, C/D area ratio, horizontal and vertical CDR were significantly (p=0.0001) higher among cases than controls. VIRA was significantly (p=0.0001) lower among cases (0.19±0.13) than controls (0.28±0.05). There was no significant (p>0.05) difference in Disc area between cases and controls [Table/Fig-5-7]. All the OCT-macular thickness parameters were significantly lower among cases than controls except fovea [Table/Fig-8,9].

OCT-ONH parameters	Cases (n=50)	Controls (n=50)	p-value[1]
Disc area (mm^2)	2.34±0.62	2.36±0.34	0.71
Cup area (mm^2)	1.33±0.34	0.75±0.27	0.0001*
Rim area (mm^2)	1.01±0.52	1.62±0.26	0.0001*
C/D area ratio	0.57±0.12	0.34±0.14	0.0001*
Horizontal CDR	0.77±0.11	0.57±0.14	0.0001*
Vertical CDR	0.77±0.11	0.57±0.14	0.0001*
VIRA (mm^2)	0.19±0.13	0.28±0.05	0.0001*

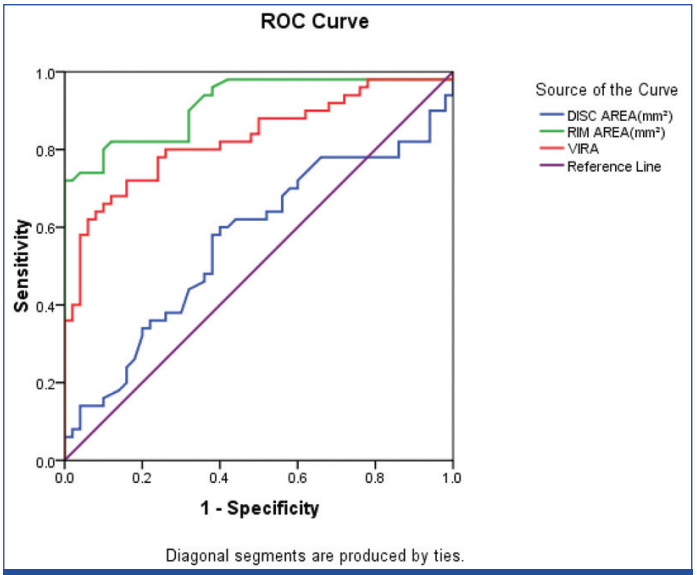
[Table/Fig-5]: Comparison of OCT-ONH parameters between the groups.
OCT: Optical coherence tomography; ONH: Optic nerve head; C/D: Cup/Disc; CDR: Cup to disc ration; VIRA: Vertically integrated rim area, [1]Unpaired t-test, *p-value <0.05 was considered statistically significant

DISCUSSION

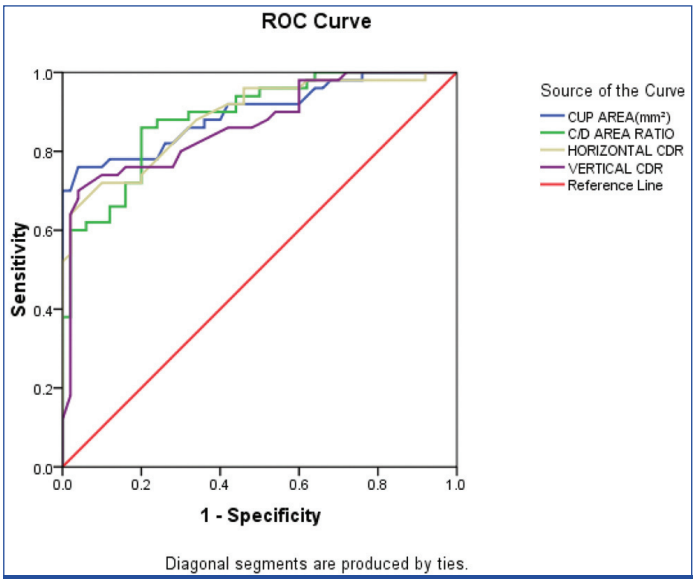
Glaucoma typically goes through several stages, from clinically nonapparent disease to irreversible blindness [11]. The diagnosis of glaucoma can often be difficult, especially in the very early stages when structural damage and functional changes are not obvious. This has led to the development of newer diagnostic modalities to reliably diagnose the disease as early as possible.

In the present study, author evaluated the ability of OCT in differentiating between early glaucomatous and healthy eyes using RNFL, ONH, and macular thickness parameters. A total of 50 cases and 50 controls were included in the study.

In the present study, the average RNFL thickness, Superior thickness, Inferior thickness and Temporal thickness were significantly (p<0.05)



[Table/Fig-6]: ROC curve showing sensitivity and specificity of OCT-ONH parameters (Disc, Rim and VIRA) in differentiating between early glaucomatous and healthy eyes.
ROC: Receiving operating curve; VIRA: Vertically integrated rim area

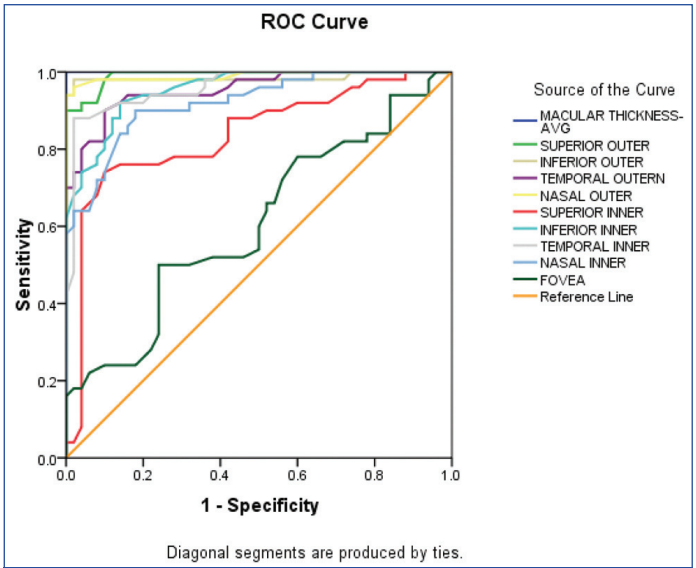


[Table/Fig-7]: ROC curve showing sensitivity and specificity of OCT-ONH parameters (Cup area, C/D area ratio, Horizontal CDR and Vertical CDR) in differentiating between early glaucomatous and healthy eyes.
ROC: Receiving operating curve; C/D: Cup/Disc; CDR: Cup to disc ration

OCT-macular thickness parameters	Cases (n=50)	Controls (n=50)	p-value[1]
Macular thickness-Average	219.88±8.15	261.34±9.59	0.0001*
Superior outer	216.30±10.80	256.28±12.65	0.0001*
Inferior outer	213.56±9.75	250.74±14.20	0.0001*
Temporal outer	216.52±12.43	246.52±12.43	0.0001*
Nasal outer	233.12±12.49	273.12±12.49	0.0001*
Superior inner	265.88±15.58	285.88±15.58	0.0001*
Inferior inner	249.50±17.79	284.50±17.79	0.0001*
Temporal inner	247.96±12.33	277.96±12.33	0.0001*
Nasal inner	260.38±15.08	290.38±15.08	0.0001*
Fovea	214.84±14.27	219.84±14.27	0.08

[Table/Fig-8]: Comparison of OCT-macular thickness parameters between the groups.
OCT: Optical coherence tomography, [1]Unpaired t-test, *p-value <0.05 was considered statistically significant

lower among cases than controls. Thickness was also lower among cases than controls at all the time periods. This was in accordance with the study of Elbendary AM and Mohamed Helal R who evaluated the role of SD-OCT in different stages of glaucoma and found similar results [12]. Abd El-Naby AE et al., found that patients with



[Table/Fig-9]: ROC curve showing sensitivity and specificity of OCT-macular thickness parameters in differentiating between early glaucomatous and healthy eyes.
ROC: Receiving operating curve; AVG: Average

glaucoma had significantly lower RNFL quadrant measurements when compared with controls in microns [7]. The present study is also in harmony with the study of Mansoori T et al., an Indian Asian study; who assessed the utility of SD-OCT to differentiate normal eyes from the early glaucomatous eyes [10]. The study recruited 178 eyes (83 patients with glaucoma and 95 age and sex matched healthy controls). The mean RNFL thickness in healthy controls and patients with glaucoma was 105.7±5.1 and 90.7±7.5 μm, respectively (p=0.001). Additionally, Kaw SMG et al., in their study compared evaluation of RNFL thickness in normal controls and POA glaucoma of various stages by SD-OCT and found that normal patients had the higher RNFL thickness as compare to patients; moreover, increased glaucoma severity was associated with thinner RNFL [13]. Moreover, the study of Firat PG et al., measured RNFL thickness in POAG, normal tension glaucoma and normal healthy individuals using SD-OCT [14]. The thickness of the RNFL was found significantly higher in normal persons, followed by the normal tension glaucoma and then in POAG (p<0.05). Furthermore, the results of the present study are in accordance with the former study of Elbendary AM and Mohamed Helal R who noted in their study that normal controls had significantly higher thickness of RNFL when compared with patients having glaucoma, and those with more severe disease had significantly thinner RNFL. The findings of this study are also in agreement with the study of Golzan SM et al., who assessed RNFL thickness in patients with glaucoma and healthy controls [12,15]. In their study, glaucomatous patients had significantly lower RNFL thickness as compare to normal patients (87±26 vs. 111±15 μm p<0.0001). The present study found that RNFL thickness parameters had a mild to moderate diagnostic value for diagnosis of early glaucoma differentiating mild glaucoma from normal controls. This is in agreement with the study of Elbendary AM and Mohamed Helal R and with a meta-analysis performed by Michelessi M et al., [12,16]. The authors illustrated the accuracy of OCT for diagnosing glaucoma. They reported that RNFL had a high accuracy for diagnosing glaucoma.

In the present study, all the macular thickness parameters were significantly (p<0.05) lower among cases than controls except fovea. Chaturvedi P et al., reported that the difference was significant in superior, nasal and inferior quadrant of macular thickness paramteres [17]. Khanal S et al., also found that there was a significant difference in Macular thickness asymmetry for all comparison groups (normal-NTG, p<0.05; normal-POAG, p<0.001; and NTG- POAG, p<0.001) [18]. In this study, all the macular thickness parameters had good diagnostic values including AUC values for diagnosis of early glaucoma differentiating glaucoma from normal controls.

In the current study, ONH parameters such as cup area, C/D area ratio, horizontal and vertical CDR were significantly (p<0.05) higher among cases than controls. The VIRA was significantly (p<0.05) lower among cases (0.19±0.13) than controls (0.28±0.05). There was no significant (p>0.05) difference in disc area between cases and controls.

In the present study, ONH parameters like disc area <2.4 mm^2 correctly predicted 30% cases with sensitivity and specificity of 60% and 58% respectively. Rim area <1.40 mm^2 correctly predicted 41% cases with sensitivity and specificity of 82% and 78% respectively. Cup area >1 mm^2 correctly predicted 39% cases with sensitivity and specificity of 78% and 76% respectively. The C/D area ratio >0.50 correctly predicted 34% cases with sensitivity and specificity of 68% and 84%, respectively.

Acquisition of 3D images of the ONH region enables us to accurately measure ONH parameters that include: disc and rim area, cup to disc ratio, cup volume and others. Mwanza JC et al., assessed the ability of SD-OCT to differentiate between glaucoma and age-matched healthy controls and reported that these ONH parameters are able to discriminate between healthy and glaucomatous eyes similar to RNFL thickness [19]. Another study done by Sung KR et al., in patients with glaucoma, preperimetric glaucoma and healthy subjects demonstrated that thickness of the RNFL was better than any tested ONH parameter [20]. The contradictory results of these two studies may be attributed due to various stages of glaucoma severity within the study samples. However, both studies reported similar diagnostic capability with rim area and average RNFL thickness in advanced glaucoma cases. The role of SD-OCT and ONH analysis in glaucoma diagnosis is yet to be determined.

In these studies, the diagnostic accuracy may not translate when used in clinical practice for diagnosis of early stage glaucoma because the discrimination studies are usually based on differentiating healthy eyes from the eyes having established glaucomatous VF loss. A SD-OCT study done by Lisboa R et al., compared the diagnostic ability of RNFL, ONH and macular parameters for diagnosing preperimetric glaucoma [21]. It was an observational cohort with 13 years of follow-up and concluded that thickness of RNFL is a better parameter than ONH and macular thickness measurements for detection of preperimetric glaucomatous damage in glaucoma suspects.

Limitation(s)

Limitation of the study was small sample size which was not sufficient for the adequate results. Future studies can be done with large sample size.

CONCLUSION(S)

At the end of the study, it was found that significant changes were present in RNFL thickness, macular thickness and ONH parameter in glaucoma cases as compare to healthy eyes and these changes can be easily assessed by OCT which is non-invasive technique. Also, a combination of RNFL and ONH parameters improved the diagnostic accuracy of OCT for detection of glaucoma. Using the above combination of parameters, detection of glaucoma can be done at an earlier stage and visual hazards can be prevented.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Mar 20, 2021
- Manual Googling: Jun 05, 2021
- iThenticate Software: Mar 27, 2021 (24%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
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- Was informed consent obtained from the subjects involved in the study? Yes
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