

DESCRIBING THE EFFECTS OF PRIMARY OPEN ANGLE GLAUCOMA ON MACULA USING SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY IN CENTRAL INDIAANJALI VIRANI¹, SHASHI JAIN², ANAMIKA TIWARI², PUJA SINGH^{4*}¹Department of Ophthalmology, Bundelkhand Medical College, Sagar, Madhya Pradesh, India. ²Department of Ophthalmology, Shyam Shah Medical College, Rewa, Madhya Pradesh, India. ³Department of Pathology, Bundelkhand Medical College, Sagar, Madhya Pradesh, India.

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ABSTRACT

Objective : Primary open-angle glaucoma is a silent predator of sight, killing retinal ganglion cells (RGCs), and leads to characteristic optic nerve head (ONH) changes and visual field (VF) defects. The conventional methods of diagnosis include clinical examination and perimetry. However, by these at the time of diagnosis, a substantial loss of RGCs has already occurred. Spectral domain optical coherence tomography (SD-OCT) allows quantitative measurements of various parameters of the retina. This tool may be utilized for selective measurement of macular parameters to make an early diagnosis of primary open angle glaucoma (POAG).

Methods: In 6 months of study, a total of 81 eyes of 51 subjects underwent SD-OCT measurements, that is, 49 eyes of 35 POAG subjects and 32 eyes of 16 age-matched healthy subjects, to record all measurable macular parameters, namely, macular thickness (MT)-central, average, in all sectors of the inner and outer circle of early treatment of diabetic retinopathy study (ETDRS) macular map; macular volume, ganglion cell-inner plexiform layer (GC-IPL) thickness-in all sectors; succeeded by statistical calculations using the unpaired t-test to calculate two-tailed p-value which is significant when its value is <0.05.

Results: As an observation the average MT, MT in the inferior and temporal sector of the inner circle of the ETDRS macular map, that in the inferior sector of the outer circle, minimum GC-IPL thickness, and GC-IPL thickness in all sectors were all significantly reduced in POAG eyes than healthy eyes. Whereas central MT, average GC-IPL thickness, macular volume, and MT in few sectors of the inner and outer circle of the ETDRS macular map proved to bear an insignificant change of POAG.

Conclusion: In this study, the greatest impact of POAG on macula was discovered in the GC-IPL layer and MT in the inferior sector of inner and outer ring which might serve the purpose of diagnosis of POAG apart from the established parameters of RNFL and ONH.

Keywords: Primary open angle glaucoma, Spectral domain optical coherence tomography, Macula, Ganglion cell-inner plexiform layer.

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INTRODUCTION

Glaucoma, a chronic optic neuropathy, is characterized by degenerations in retinal ganglion cells (RGCs) leading to progressive atrophy in optic nerve head (ONH) and VF defects detected in perimetry; which may cause profound visual loss if not treated on time [1].

It's estimated global prevalence is over 70 million making glaucoma one of the leading causes of irreversible blindness [2]. Furthermore, it is a common knowledge that about 10% of patients of glaucoma are bilaterally blind which makes it a huge public health problem [3]. Adding to the above, among the 12 million diagnosed patients of glaucoma in India nearly 1.2 million are blind, which is 10% [4].

Primary open angle glaucoma (POAG) accounts for a major proportion of glaucoma patients, although there are differences in data per studies. Usually bilateral, it is a creeping disease which remains asymptomatic in its most treatable stages and so the likelihood of a diagnosis in a very advanced stage is as high as 40% [5-7]. Although it causes irreversible blindness in patients with late stages of diagnosis, it is possibly preventable with early diagnosis, good treatment, and patient compliance.

Selective retinal ganglion cell loss is the pathological hallmark of glaucomatous optic neuropathy which begins at the optic disc lamina, as it gets compressed and deformed by intraocular pressure (IOP), of which axonal damage is a consequence [8]. This manifests in the form of characteristic ONH changes, corresponding VF defects and retinal nerve fiber layer (RNFL) loss [9].

Standard automated perimetry is the gold standard diagnostic test for glaucomatous optic neuropathy which detects visual field defects only after an immense loss of about 30-50% of RGCs [9]. Therefore identifying RGC loss at the earliest is of paramount importance to prevent the development of irreversible visual field defects. Here spectral domain optical coherence tomography (SD-OCT) comes to play a critical role of detection RGC loss before it could be diagnosed by the conventional methods with an added advantage of quantitative assessment through several parameters linked to glaucoma [10,11].

OCT, a non-invasive diagnostic technique, works on the concept of interferometry and generates *in vivo* cross-sectional pictures of the retina, accurate to within at least 10-15 microns [12] making it a valuable instrument for monitoring glaucomatous structural changes [13]. The development of spectral domain OCT (SD-OCT) with enhanced axial resolution and scan speed, the capability of OCT to assess macular thickness (MT) has increased further which is highly reproducible, with low intravisit and intervisit variations [14-16] allowing easier detection of glaucomatous progression.

Macula, the only place in retina where RGC bodies are stacked up to six layers thick, constitutes more than 50% of the RGCs of the entire retina. Since the RNFL comprises of the RGC axons; therefore, assessment of the RGCs may be a more direct method of evaluation of glaucomatous damage than peripapillary RNFL (ppRNFL) thickness, also the cell body is substantially larger than the axons of the RGCs which makes more part of the thickness than the axon does and thus might improve the

ability to detect damage to these cells [10,17,18]. Allowing scanning and accurate quantitative assessment of the macula, optical coherence tomography aids sampling of the majority of the RGCs.

MT evaluation received gross attention after Zeimer *et al.* [17] hypothesized that quantitative detection of glaucomatous damage at macula may provide a method for detection and monitoring of early glaucomatous damage. Although some studies favor MT as a valuable surrogate measure for evaluating glaucomatous structural changes, the presence of contrasting reports on its discriminating power and reproducibility is ordinary.

In this study, we aim to measure the macular parameters in primary open-angle glaucoma patients (POAG) and in healthy controls (N) using SD-OCT and investigate the diagnostic performance of macular parameters in primary open angle gaucoma.

Aims and objectives

- The objectives of the study are as follows: To record retinal macular measurements in eyes of primary open angle gaucoma subjects and healthy subjects using SD-OCT
- To compare both group's data on SD-OCT and interpret changes induced in macula of eyes with primary open angle gaucoma

METHODS

The study was carried out on a total of 81 eyes of 51 subjects comprising of 49 eyes of 35 POAG patients and 32 eyes of 16 healthy subjects with no eye disease, in the ophthalmology department of a tertiary care center. The patients were recruited from the outpatient department of the same center from January 2019 to June 2019. Ethical clearance has been obtained from the Institutional Ethical Committee no. 29/SS/MC/18.

To verify the diagnosis of primary open angle gaucoma, after taking informed consent, the patient underwent the following examinations: Detailed ophthalmic and medical history, best corrected visual acuity using Snellen's self-illuminated chart, IOP measurement by non-contact tonometer, slit lamp examination by Zeiss slit lamp to exclude presence of any anterior segment abnormalities, gonioscopy by Volk single mirror gonioscope to ensure open angle of anterior chamber, direct ophthalmoscopy using Heine beta 200 direct ophthalmoscope to assess media clarity, and evaluate posterior pole preliminarily followed by slit lamp indirect ophthalmoscopy with Volk +90D lens. Automated perimetry was conducted thereafter to assess the VF defects which was superseded by spectral domain-optical coherence tomography (CIRRUS HD-OCT) that scanned the macula to measure their parameters, namely, MT, macular volume, and ganglion cell-inner plexiform layer (GC-IPL) thickness.

POAG cases had intra-ocular pressure >21 mmHg without medication, no anterior segment abnormalities, open angle on gonioscopy, characteristic ONH changes, reliable VF testing, absence of other ophthalmic or neurologic diseases causing VF defects other than glaucoma, and absence of apparent pathological changes in the macula, for example, age-related macular degeneration, etc.

The controls or normals had no any signs of an ongoing or established ophthalmic disease in the anterior or posterior segment and had absolutely normal VFs.

OCT measurements

Subjects were scanned with SD-OCT (CIRRUS HD OCT MODEL 500). Scan protocol of Cirrus HD OCT called macular cube 516 × 258 protocol was used for macular scanning. MT measured in early treatment of diabetic retinopathy study (ETDRS) circle (Fig. 1) of 6 × 6 mm² which is further divided into nine areas by two inner circles (2 and 4 mm diameter, respectively) and sectoral partitions and ganglion cell OU measured in 6 × 6 mm cube and contained an elliptical annulus centered about the fovea. Sectors divide GC-IPL thickness map into six regions, three equally sized sectors in superior region and three equally sized sectors in inferior region. Macular volume is also recorded.

Statistical analysis

For our present study, the data were fed in MS Excel, mean and standard deviation were calculated, p-values were derived through unpaired t-test, Statistical Graph Pad InStat version 3.06. p<0.05, that is, <5% error is considered statistically significant.

OBSERVATION AND RESULTS

With respect to the inclusion and exclusion criteria, 49 eyes of POAG patients were recruited for the study against 32 eyes of age and sex-matched healthy controls which underwent a battery of evaluation techniques and compared with each other further on the basis of recorded data. All subjects under study underwent SD-OCT examination on which it was found that the optic discs of eyes with POAG had significantly thinner circumpapillary RNFL in all quadrants (Fig. 2) as compared to normal patients (Fig. 3) and on average which is already known and applied fact in the diagnosis of POAG.

Per study macular parameters were measured on OCT (Fig. 4) and a color coded ETDRS macular map was obtained (Fig. 5). It was also discovered that a similar effect to that of RNFL was found in a few sectors of ETDRS MT map (Table 1) and GC-IPL thickness in the macula of retina (Table 3).

However, macular volume showed insignificant differences from normal as a result of retinal ganglion cell loss.

GC-IPL thickness was measured in terms of average, minimum, and thickness in all six sectors, that is, superior, inferior, superonasal,

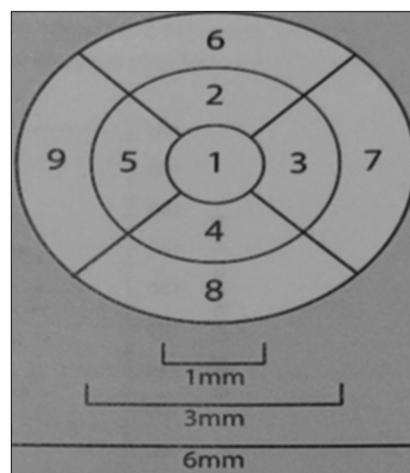


Fig. 1: Early treatment of diabetic retinopathy study macular map

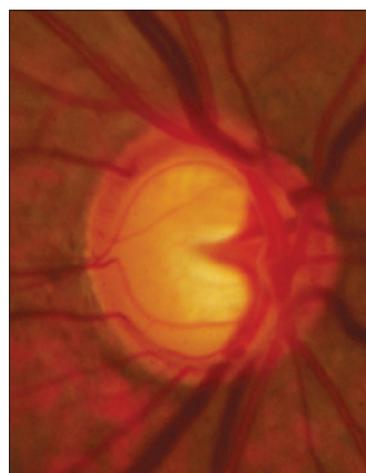


Fig. 2: Advanced glaucomatous optic disc

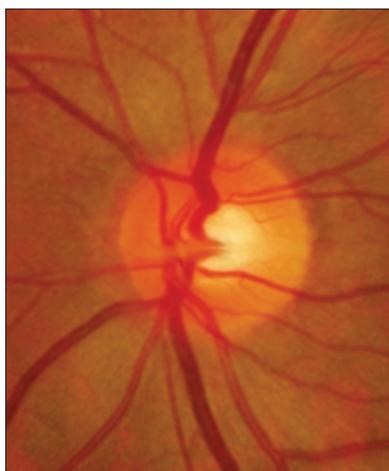


Fig. 3: Normal optic disc



Fig. 5: Color-coded early treatment of diabetic retinopathy study macular thickness map

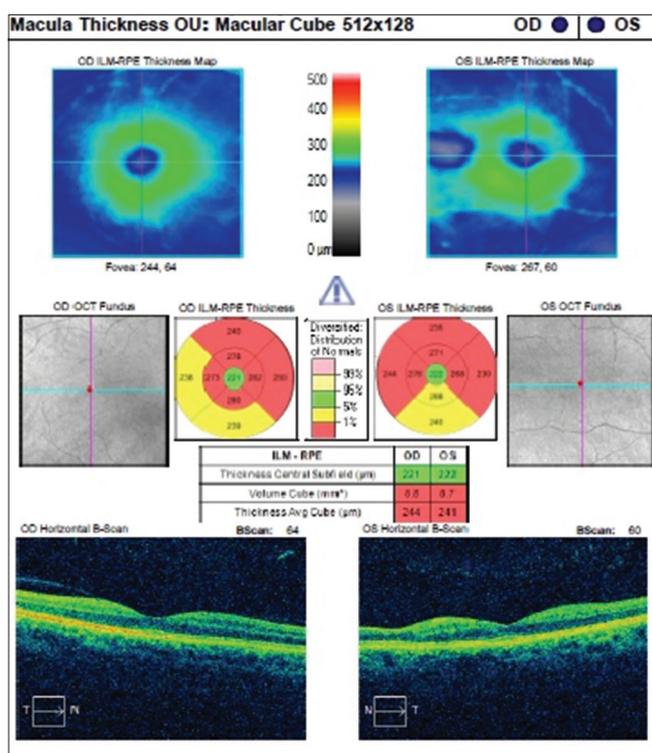


Fig. 4: Optical coherence tomography picture of macular cube

inferonasal, superotemporal, and inferotemporal. Thickness of GC-IPL was decreased significantly in all sectors and minimum GC-IPL was also low in eyes with POAG but the significance of difference in average GC-IPL could not be proved.

DISCUSSION

It is a fact that after a serious amount of loss in retinal nerve fiber layer (RNFL) functional loss becomes apparent in perimetry which is diagnosable and it becomes obvious that to diagnose and treat glaucoma, perimetry alone is not enough. Diurnal variation in IOP, the sensitivity of the optic nerve to increase in IOP together exhibits considerable differences between individuals. Therefore, the importance of IOP in diagnosis of glaucoma becomes controversial with developing technologies [12]. Another point in diagnosis of glaucoma is clinical fundus examination highlighting ONH and RNFL which is highly subjective and causes interobserver as well as intervisit variations [13]. Therefore, objective and quantitative assessment of

Table 1: Values of macular thickness on ETDRS macular map as measured by cirrus HD-OCT

Macular thickness	Thickness±SD		p-value
	POAG	Control	
Average	255.04±21.48	264.25±10.32	0.0509
Central	237.51±25.41	255.57±16.11	0.0019
Inner superior	296.22±24.66	310.25±11.85	0.1219
Inner inferior	285.46±28.48	313.5±12.61	0.0086
Inner temporal	278.38±30.01	294.87±8.13	0.137
Inner nasal	294.06±32.84	320.25±13.14	0.0311
Outer superior	251.48±33.17	266.25±8.01	0.2185
Outer inferior	243.63±23.98	263.87±10.41	0.0231
Outer temporal	242.87±18.47	251.375±11.04	0.2129
Outer nasal	273.61±27.90	287.25±7.72	0.1779

Table 2: Values of macular volume as measured by cirrus HD-OCT

???	POAG	Control	p-value
Macular volume	9.48±0.75	9.68±0.5	0.1196

Table 3: Values of GC-IPL thickness as measured by cirrus HD-OCT

GC-IPL	Average thickness±SD		p-value
	POAG	Control	
Average	70.89±40.2	80.13±5.13	0.3459
Minimum	53.76±17.34	74.39±4.27	<0.0001
Superior	66.36±14.37	83.34±3.17	<0.0001
Superonasal	67.46±18.20	82.91±5.07	<0.0001
Superotemporal	61.91±14.74	78.78±5.25	<0.0001

ONH and RNFL becomes critically important and is aided by machines such as OCT.

Guedes et al. [19] studied 534 eyes of 367 subjects in Boston, categorized as normal (166 eyes of 109), glaucoma suspects (83 eyes of 58), early glaucoma (196 eyes of 132), and advanced glaucoma (89 eyes of 68). Using OCT, (prototype and commercial [OCT1, Zeiss-Humphrey, Dublin, CA]) measurements, macular, and nerve fiber layer (NFL) thickness were carried out and analysis of their correlation with each other and with glaucoma status was done. NFL thickness was observed to be statistically significantly different between normal (113.6±15.8)

and either of early (94.7 ± 22.2) or advanced glaucoma (64.3 ± 27.3) subjects ($p < 0.001$). Although MT (Inner, outer ring, and mean) was also significantly different between normal and advanced glaucomatous eyes ($p < 0.001$), only outer ring thickness could significantly differentiate between normal (230.4 ± 14.9) and early glaucoma (224.5 ± 15.8) ($p = 0.003$, $p = 0.008$, respectively).

They concluded that statistically significant correlations with glaucoma were found with both macular and NFL thickness, although NFL thickness had a stronger association.

Our study is in accordance with the Zeimer *et al.* [17] hypothesis of decreasing macular volume with advancing disease. Giovannini *et al.* [20], Parikh *et al.* [21], Sharma *et al.* [22], Khanal *et al.* [23], and Lederer *et al.* [24] found results consistent to ours among POAG and control groups whereas Lederer *et al.* [24] in the same study did not find variation significant enough among POAG suspects and controls where though the inclusion criteria and methods were similar, the calculation of macular volume was performed manually after estimation of MT from commercially available OCT1 machine.

Parikh *et al.* [21] assessed 121 eyes of 121 patients in LV Prasad Eye Institute, Hyderabad, divided into two groups: Early glaucoma {56 eyes of 56 patients} and normal {75 eyes of 75 patients} who underwent imaging with Stratus OCT 3, version 4 (Carl Zeiss, Dublin, California). The MT map included nine sectors – the fovea, inner macula, and outer macula, with diameters of 1, 3, and 6 mm. Sensitivity, specificity, area under the receiving operating characteristic curve (AUROC), and likelihood ratio were calculated for volume and thickness parameters in these nine sectors.

Two parameters, namely, the outer inferior average volume (1.09 ± 0.07) ($p < 0.0026$) and the outer inferior average thickness (205.50 ± 12.40) ($p < 0.002$), exhibited statistically significantly lower values in the glaucoma group (1.05 ± 0.10 , $p = 0.0026$) (197.00 ± 18.25 , $p = 0.002$) of which outer inferior average volume (1.05 ± 0.10 , $p = 0.0026$) had the “best combination” of sensitivity and specificity (56% and 79% respectively). Both parameters yielded the best AUROCs of 0.66.

Therefore, they deduced that outer inferior MT and volume parameters in early glaucoma are significantly different from normal and can have a role in the diagnosis of early glaucoma.

Nakatani *et al.* [25] assessed one eye each from 32 early glaucoma patients (including preperimetric glaucoma) and 32 normal participants in Japan; who underwent macular scans and ppRNFL scans by SD-OCT imaging using 3D-OCT-1000 Mark II (3D-OCT, Topcon, Tokyo, Japan). The discrimination power of each parameter to detect early glaucoma was determined by areas under receiver operating characteristics curve (AROC) and sensitivity at fixed specificity. There were significant differences between early glaucoma and normal participants for all parameters except fovea in macular scans and in the superior and inferior quadrants, at 12, 3, 6, 7, 11 o'clock, and average RNFL thickness in RNFL scans. The best parameters based on AROC and sensitivity at a specificity of >90% were temporal outer macula thickness (N [244.5 ± 10.3], POAG [232.0 ± 11.3] $p \leq 0.001$) (AROC 0.79; sensitivity 63%) in macular parameters and inferior quadrant (N [133.8 ± 15.4], POAG [112.1 ± 19.1] $p \leq 0.001$) (AROC 0.82; sensitivity 53%) in RNFL parameters. They concluded that in diagnosis of early glaucoma by SD-OCT, macular parameters had high discriminating power and high reproducibility comparable with ppRNFL parameters.

Kotera *et al.* [26] in their study in Kyoto, Japan, included 30 eyes with suspected glaucoma and preperimetric glaucoma (SGPPG) and 35 healthy eyes. The MT, including those of the total retina, nerve fiber layer (NFL), and combined inner retinal layers (IRLs) – NFL, ganglion cell layer (GCL), and IPL – was measured by 3D-OCT-1000 (Topcon Corp., Tokyo, Japan) raster scans in a 6 mm² region. The average and

sectoral thicknesses were calculated on an ETDRS chart and a ETDRS chart with a 45° rotation (glaucoma sector chart, GSC).

The mean IRL thickness was significantly less in the SGPPG eyes (99.7 ± 8.2) ($p = 0.001$) than in the healthy eyes (106.9 ± 7.6) ($p = 0.001$), but the mean total retinal and macular NFL thicknesses were not. In the SGPPG eyes, the IRLs were thinner in the outer macula (96.4 ± 8.2) ($p < 0.0001$) than in the inner macula (110.5 ± 9.5) ($p = 0.311$), in the inferior hemisphere (97.9 ± 8.2) ($p < 0.0001$) than in the superior hemisphere (101.3 ± 9.7) ($p = 0.015$) and in the temporal hemisphere than in the nasal hemisphere. The IRLs in the inferior temporal outer sector (95.0 ± 8.5) ($p < 0.0001$) (AROC–0.86) (GSC) had the greatest area under the receiver operating characteristic curve, which was significantly greater than those for the IRLs over the entire macula (99.7 ± 8.2) ($p = 0.001$) (AROC–0.74), inferior hemiretinal region (97.9 ± 8.2) ($p < 0.0001$) (AROC–0.78) and inferior outer hemicircular region (95.0 ± 8.5) ($p < 0.0001$) (AROC–0.81) and that for the circumpapillary NFL in the inferior sectors (112.1 ± 14.7) ($p = 0.004$) (AROC–0.71).

Thus, the macular IRL thickness measured using 3D-SD-OCT is useful for profiling macular atrophy in SGPPG.

Lee *et al.* [27] reported macular OCT-VF relationships have localized arcuate characteristics in the central region of the macula. Given the overlapping nature of structure-function relationships, a smaller number of VF test locations may be used to summarize macular functional damage.

Zhang *et al.* [28] reported that OCT is more sensitive than VF for the detection of progression in early glaucoma.

Ojima *et al.* [29] reported a significant decrease in six of nine macula segments at early stage of glaucoma and normal foveal thickness even at late stages.

CONCLUSION

With the established parameters of diagnosis of glaucoma, losing a significant amount of vision is known. OCT introduces as a revolutionary tool that can reliably and reproducibly measure retinal thickness as a whole and segmented. Using the above quality of tool, it is possible to make glaucoma diagnosis simpler and quicker and most importantly on time which means, we can prevent the loss of vision caused. In this study, we measured and evaluated the macular parameters in POAG patients. The greatest impact of POAG on macula was discovered in GCIPL layer ($p < 0.0001$) and MT in inferior sector of inner and outer ring. These parameters have never been used for diagnosing glaucoma but if used might serve the purpose of early diagnosis of POAG apart from the established parameters of RNFL and ONH as well as prevent or slow down the progression of glaucoma with treatment.

CONFLICTS OF INTEREST

None declared.

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Nil.

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