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Research Article

DISCRIMINATION OF EYES WITH PRIMARY OPEN-ANGLE GLAUCOMA FROM NORMAL USING MACULAR GC-IPL THICKNESS

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ABSTRACT

Objective: Primary open-angle glaucoma (POAG), a neuro-ophthalmological disease, is a condition of slowly progressive loss of retinal ganglion cells which are evident as characteristic optic nerve head vicissitudes and visual field defects, only after death of more than 40% of cells. This huge loss when witnessed is started to treat only if the patient approaches an ophthalmologist with a significant complaint, leading to optic nerve head examination, which means being an asymptomatic disease, it is usually left undiagnosed until advanced. An additional system of diagnosis of the disease earlier in the stage can aid reduce the burden of the blindness of POAG.

Methods: Among a total of 62 eyes of 31 subjects, 40 eyes of 20 POAG subjects, and 22 eyes of 11 age-matched healthy subjects were recruited. All of them underwent Spectral Domain Optical Coherence Tomography macular and optic disk scans to note macular ganglion cell–inner plexiform layer (mGCIPL) and retinal nerve fiber layer (RNFL) thicknesses. Statistical analysis was did using an unpaired t-test and calculating a two-tailed p value, in which the significance was indicated by $p<0.05$.

Results: Similar to peripapillary RNFL thickness, the mGCIPL parameters, that is, minimum GCIPL thickness and GCIPL thickness in all sectors decreased significantly in POAG eyes to be able to discriminate them from normal. mGCIPL and RNFL thickness decreased as the severity of glaucoma increased.

Conclusion: The minimum GCIPL thickness and that in all sectors can discriminate POAG eyes from healthy eyes significantly and has comparable performance to that of peripapillary RNFL thickness.

Keywords: OPEN-ANGLE GLAUCOMA, MACULAR GC-IPL Thickness, Retinal nerve fiber layer, Spectral Domain Optical Coherence Tomography.

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INTRODUCTION

A progressive disease in which selective apoptosis of retinal ganglion cells (RGCs) result in retinal nerve fiber loss leading to characteristic optic nerve head (ONH) changes and visual field (VF) defects is known as Glaucoma and can ultimately result in blindness [1-3].

Of all the known types of glaucoma, primary open-angle glaucoma (POAG) accounts for a major proportion and is usually bilateral. Known to be a creeping disease, it remains asymptomatic in its most treatable stages, and so, it is diagnosed very late in nearly 40% of cases [4-6]. Before becoming clinically apparent, about 40–60% loss of retinal nerve fiber layer (RNFL) and development of VF scotomas has already occurred. POAG keeps developing insidiously over years hindering the clinical diagnosis on time [7]. This may lead to irreversible blindness, a blindness that has no cure in advanced stages of diagnosis and which can be readily prevented or slowed down by an early diagnosis.

RGC bodies vary in the number of layers at varied areas of the retina, being maximum at the macula. The macula is the only part of the retina that comprises nearly six stacked-up layers of RGCs which are about 50% of the total RGCs in the retina. The RNFL is the RGC axons, so if the cell bodies die even the axons do not survive. Loss of RGC axons is apparent as characteristic ONH appearance or RNFL wedge defects, and therefore, loss of the RGCs may be assessed better directly by measurement of RGC layer thickness. As the cell body is substantially larger than the axons of the RGCs, it makes more part of the thickness than the axon does and, thus, might improve the ability to detect damage to these cells [8-10].

Optical coherence tomography (OCT) machine measures the thickness of the ganglion cell–inner plexiform layer (GC-IPL) at the macula and the RNFL in the peripapillary region of the retina [11-13]. Increasing the image resolution of OCT enables it to measure the thickness of all retinal layers as well as monitor their changes over time. Spectral-domain (SD)-OCT can determine the macular and ONH parameters with good repeatability and reproducibility [14]. The previous studies report decreased RNFL, ganglion cell layer (GCL), and inner plexiform layer (IPL) thickness as a sign of glaucomatous damage, while the outer retinal layers do not exhibit significant change [15-17]. Allowing scanning and accurate quantitative assessment of the macula, OCT aids in the sampling of the majority of the RGCs.

Aims and objectives

The aims of this study were as follows:

- To record macular GCIPL (mGCIPL) thickness and peripapillary RNFL thickness in healthy and POAG eyes using SD-OCT
- Compare the measured parameters among both groups
- Determine the discriminating power of mGCIPL thickness amid healthy eyes with POAG.

METHODS

The study was approved out on a total of 62 eyes of 31 subjects comprising 40 eyes of 20 POAG patients and 22 eyes of subjects with normal eyes, in the ophthalmology department of a tertiary care center in central India. The patients were recruited from the outpatient department of the same center from January 2021 to June 2021.

To verify the diagnosis of POAG, after taking informed consent, the patient underwent the following examinations:

1. Detailed ophthalmic and medical history
2. Best-corrected visual acuity using Snellen's self-illuminated chart

3. Intraocular pressure (IOP) measurement by non-contact tonometer
4. Slit-lamp examination by Zeiss slit-lamp to exclude the presence of any anterior segment abnormalities
5. Gonioscopy by Volk single mirror goniolens to ensure the open-angle of the anterior chamber
6. Direct ophthalmoscopy using Heine beta 200 direct ophthalmoscopes to assess media clarity and evaluate posterior pole preliminarily followed by slit-lamp indirect ophthalmoscopy with Volk +90D lens
7. Automated perimetry was conducted to assess the VF defects
8. SD-OCT (CIRRUS high definition OCT [HD-OCT]) scanned the ONH and macula to measure their parameters, namely, vertical cup-disk ratio, rim area, cup volume, circum-papillary RNFL thickness, macular thickness, macular volume, and GC-IPL thickness.

Selection criterion regarding test subjects is as follows:

1. POAG cases:
   a. IOP >21 mmHg without medication
   b. No anterior segment abnormalities
   c. Open-angle on gonioscopy
   d. Characteristic ONH changes
   e. Reliable VF testing
   f. Absence of other ophthalmic or neurologic diseases producing VF defects other than glaucoma
   g. Absence of apparent pathological deviations of the macula, for example, ARMD.
2. Control/normal cases:
   a. IOP within a normal range of 10–21 mm of Hg
   b. No signs of any ophthalmic disease, ongoing or old, in the anterior or posterior segment
   c. Open-angle on gonioscopy
   d. Normal-appearing ONHs
   e. VF tests were normal, that is, devoid of any scotomas.

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. Ganglion cell OU measured in a 6×6 mm cube and contained an elliptical annulus centered about the fovea. Sectors divide the thickness map into six regions three equally sized sectors in the superior region and three equally sized sectors in the inferior region (Fig. 1).

Statistical analysis

For our study, the data were fed in MS Excel, mean and standard deviation were calculated, and 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.

RESULTS

For the inclusion and exclusion criteria, 40 eyes of POAG patients were recruited for the study and compared with 22 eyes of age- and sex-matched healthy controls.

After SD-OCT scanning of all the study subjects, a color-coded map of RNFL thickness and GC-IPL thickness was generated (Figs. 2 and 3). It was found that the eyes with POAG had significantly thinner circum-papillary RNFL, particularly in superior and inferior quadrants and on average (Table 1). It was also discovered that a similar effect was found on the GC-IPL thickness of a few sectors in the macula of the retina (Table 2).

GC-IPL thickness was measured in terms of average, thickness in all six sectors (Fig. 1), that is, superior, inferior, superonasal (SN), inferonasal (IN), superotemporal (ST), and inferotemporal (IT). The thickness of GC-IPL was significantly decreased in inferior, ST, and IT sectors, whereas the others did not bear a significant change.

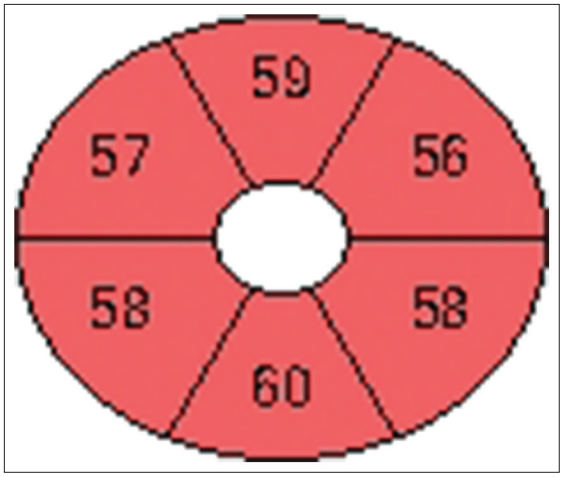

Fig. 1: Ganglion cell–inner plexiform layer thickness in the elliptical annulus

Table 1: RNFL thickness

RNFL	Thickness±SD		p-value
	POAG	Control	
Average	72.09±22.78	98.77±7.93	<0.0001
Superior	76±26.80	127.77±15.45	<0.0001
Inferior	79.27±27.28	130.05±15.72	<0.0001
Temporal	59.07±17.58	61.27±10.36	0.6154
Nasal	69.62±16.99	76.11±10.41	0.1115

RFNL: Retinal nerve fiber layer, POAG: Primary open-angle Glaucoma

Table 2: GC-IPL thickness

GC-IPL	Thickness±SD		p-value
	POAG	Control	
Average	70.89±40.2	80.13±5.13	0.3459
Superior	78.9±14.37	83.34±3.17	0.1593
Superonasal	78.46±18.20	82.91±5.07	0.2674
Superotemporal	61.91±14.74	78.78±5.25	<0.0001
Inferior	61.25±16.03	76.26±12.54	<0.0001
Inferonasal	76.55±16.23	81.73±5.36	0.1524
Inferotemporal	58.89±16.07	79.52±7.38	<0.0001

GC-IPL: Ganglion cell–inner plexiform layer, POAG: Primary open-angle glaucoma

DISCUSSION

The obtainable work indicates the impact of glaucoma on the central retinal architecture in the study population of central India in a tertiary care center, affected by POAG in various stages of the disease. POAG has a strong impact on the inner retinal layers (IRLs) of the retina, that is, RNFL and GC-IPL, whereas the impact on the outer retinal layers is minimal, and so, the calculation of thickness of IRLs may aid in its early diagnosis, diagnosis in conditions with abnormal ONH, and monitoring of glaucoma progression.

In their study, Kotera *et al*., in Kyoto, Japan, included 30 eyes with suspected glaucoma and preperimetric glaucoma (SGPPG) and 35 healthy eyes. The macular thickness, including those of the total retina, nerve fiber layer (NFL), and combined IRLs–NFL, GCL, IPL – was measured by 3D-OCT-1000. (Topcon Corp., Tokyo, Japan) raster scans in a 6 mm^2 region. The average and sectoral thicknesses were calculated on an early treatment of diabetic retinopathy study (ETDRS) chart and an ETDRS chart with a 45° rotation (glaucoma sector chart, GSC) [18].

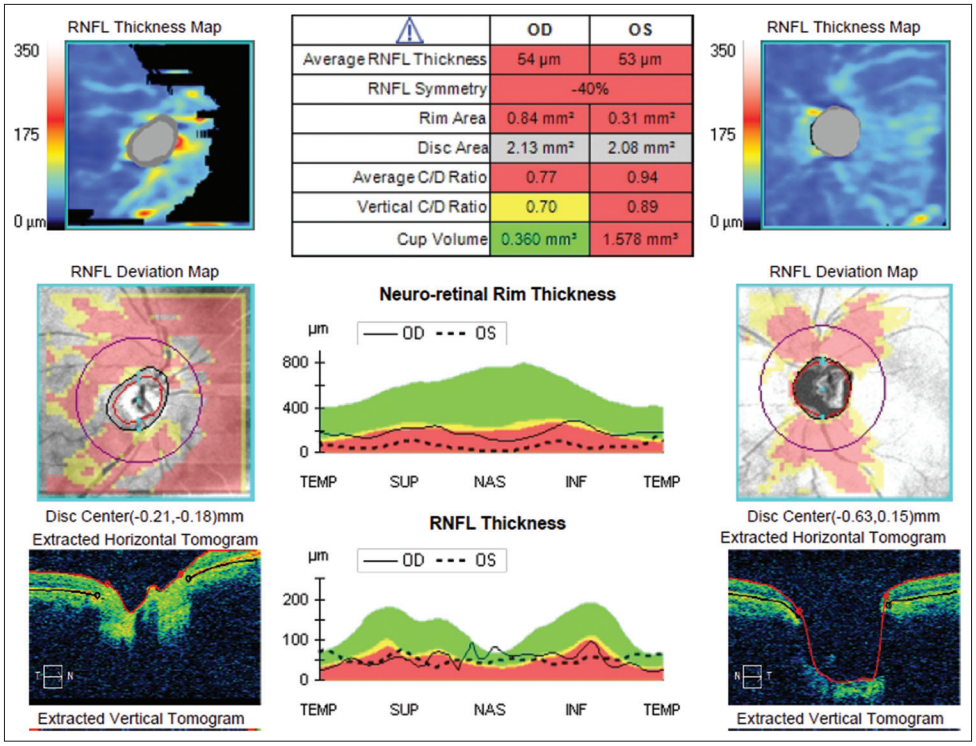

Fig. 2: Retinal nerve fiber layer thickness scan

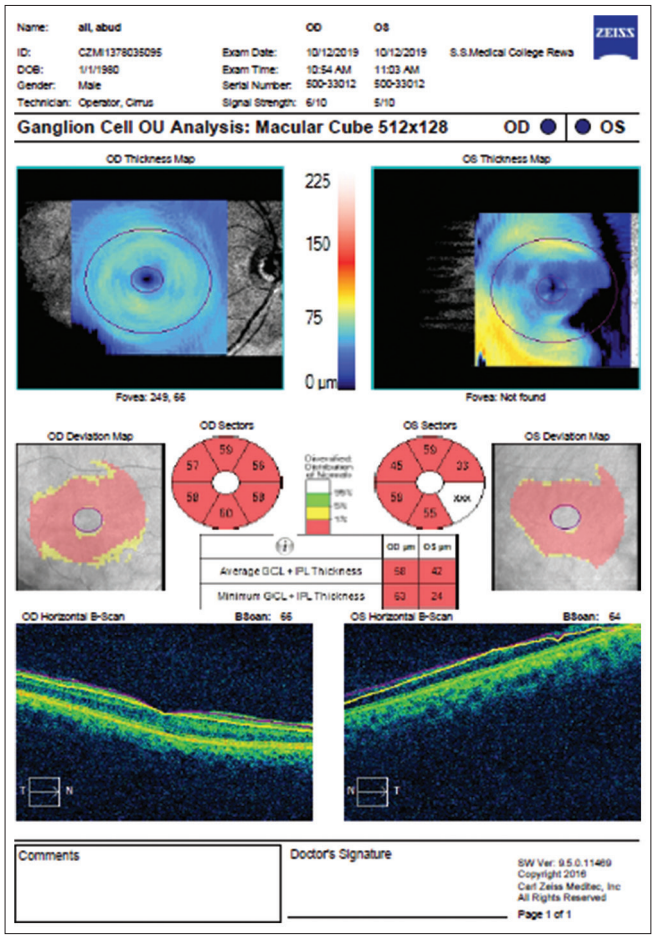

Fig. 3: Ganglion cell–inner plexiform layer thickness scan

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) [18].

Thus, the macular IRL thickness measured using 3D-SD-OCT is useful for profiling macular atrophy in SGPPG [18].

In their study, Na *et al*. evaluated 141 glaucomatous and 61 healthy eyes in Korea. All glaucomatous eyes were subjected to SD-OCT examinations using Cirrus HD-OCT (GCA; Carl Zeiss Meditec, Dublin, CA). Segmented macular layers were the macular NFL, ganglion cell and IPL (GCA), and outer retinal layer (from outer plexiform layer to retinal pigment epithelium). Areas under receiver operating characteristic curves (AUCs) discriminating healthy from glaucomatous eyes were determined in baseline measurements. The sensitivity and specificity of these parameters in terms of glaucoma progression detection were determined, with reference to the assessment of optic disc/RNFL photographs/VF deterioration as standard(s) [19].

GCA afforded the best diagnostic performance among three macular parameters. The AUC of the GCA thickness (GCAT) was less than that of cRNFLT (0.869 vs. 0.953, p¼0.018), but superior to that of TMT (0.790, p¼0.05). Of the eyes, 38 showed progression during follow-up by

standard methods. The sensitivities of TMT, GCAT, and cRNFLT values in terms of detection of progression were 14%, 8%, and 5%, respectively, with no statistical significance [19].

They concluded that although baseline cRNFL measurement was optimal in terms of glaucoma diagnosis, the GCAT and TMT showed similar levels of sensitivity in progression detection. Baseline GCA thickness differed significantly between glaucomatous (73.03±10.10) ($p<0.001$) and healthy eyes (84.93±64.77) ($p<0.001$) as well as healthy (84.93±64.77) ($p<0.001$) and preperimetric eyes (78.64±7.24) ($p<0.001$), suggesting that GCA thickness might serve as an early indicator of glaucomatous structural damage [19].

In their study, Pazos *et al*. assessed 40 early glaucoma eyes and 40 healthy controls. All members were examined using the normal posterior pole and the peripapillary RNFL (pRNFL) procedures of the Spectralis OCT (Heidelberg Engineering, Inc., Heidelberg, Germany) device. Using an Early Action Analytic Retinopathy Study circle at the macular level, the automated retinal segmentation software was practical to determine thicknesses of the succeeding parameters: total retinal thickness, inward retinal layer (IRL), macular RNFL (mRNFL), macular GCL (mGCL), macular inner plexiform layer (mIPL), macular inner nuclear layer, macular outer plexiform film, macular outer nuclear sheet, photoreceptors, and retinal pigmentary epithelium. The ganglion lockup complex (GCC) was determined by adding the mRNFL, mGCL, and mIPL parameters and the ganglion cell layer inner plexiform layer (mGCLIPL) was determined by uniting the mGCL and mIPL limits. The thickness of each layer remained compared between the groups, and the layer and sector with the best area under the receiver operating characteristic curve (AUC) were identified [20].

On comparison, they observed that peripapillary RNFL was significantly thinner in the EG group globally and in all six sectors assessed ($p<0.0005$). For the macular variables, total retinal thickness was significantly reduced in the EG group [20].

They concluded that macular intraretinal measurements still have not overcome standard pRNFL parameters [20].

In their study, Vercellin *et al*., in Massachusetts, United States, studied 672 subjects, 101 open-angle glaucoma (29 with early glaucoma) and 571 healthy who underwent peripapillary RNFL thickness and 3D macular volume scans using Spectralis OCT (HRA/Spectralis software version 5.4.8.0, Heidelberg Engineering GmbH). Parameters calculated were: total macular thickness (M-thickness), total macular volume (M-volume), ganglion cell multipart (GCC) depth, and GCC volume of the innermost three macular layers (RNFL+ganglion cell layer+inner plexiform layer), each for six different-sized annuli. The best diagnostically performing macular parameter was GCC-volume-34, with an inner diameter of 3 mm and an exterior of 4 mm. Statistically, similar AUROC was obtained for RNFL thickness and GCC-volume-34 for all areas (global: RNFL thickness 0.956, GCC-volume-34 0.939, p value ¼ 0.3827), but for the chronological GCC-volume-34, which was significantly better than temporal RNFL thickness (p value ¼ 0.0067). They concluded that the best macular parameters (GCC-volume-34 and GCC-thickness-34) had similar to or better diagnostic performance than that of 2D RNFL thickness [21, 22].

In their study, Lin PW *et al*. evaluated 145 patients, 53 with POAG, 60 with normal tension glaucoma, and 32 with normal controls in Kaohsiung, Taiwan. SD-OCT imaging was performed with the Spectralis OCT (Heidelberg Engineering, Dossenheim Heidelberg, Germany) for assessing the thicknesses of pRNFL, total macular layers, and inner macular layers (IML), which include mRNFL and mGCL. The mGCL thickness significantly correlated with the pRNFL thickness in the superior and inferior quadrants ($R2=0.156$, $p<0.001$; $R2=0.407$, $p<0.001$). AROC was greater for the thickness of the inferior-outer sector of macula than for the inferior-inner sector. AROCs were similar for superior (0.894) and inferior (0.879) pRNFL thicknesses and superior (0.839) and inferior mGCL (0.864) thicknesses [23].

They concluded that the diagnostic capability of the mGCL thickness is comparable to that of the pRNFL thickness in patients with the early glaucoma, whereas the inferior-outer sector of IML has a better diagnostic capability than the inferior inner sector of IML for the same [23].

In their study, Ustaoglu *et al*. evaluated 147 eyes (40 healthy, 40 glaucoma suspects, 40 early glaucoma, and 27 moderate-to-severe glaucoma) of 133 subjects in Turkey. Using Cirrus HD-OCT 5000 (Carl Zeiss Meditec), GC-IPL, RNFL, and ONH parameters were measured and evaluated by determining the area under the curve (AUC) of the receiver operating characteristics [24].

All GC-IPL parameters discriminated glaucoma suspects from healthy ($p<0.017$) and moderate-to-severe glaucoma from the early glaucoma patients ($p<0.017$). The minimum, inferotemporal, and IN GC-IPL parameters discriminated early glaucoma from glaucoma suspects, whereas no RNFL or ONH parameter could do so. Superonasal GC-IPL, superior RNFL, and average c/d ratio (AUC=0.746, 0.810, and 0.746, respectively) were the best parameters to discriminate glaucoma suspects from healthy eyes. Discriminating performances of all the parameters were lower than that of the other consecutive group comparisons for the early glaucoma versus glaucoma suspect comparison, with the best GC-IPL parameters being minimum and inferotemporal (AUC=0.669 and 0.662, respectively). Minimum GC-IPL, average RNFL, and rim area (AUC=0.900, 0.858, and 0.768, respectively) were found to be the best parameters for discriminating moderate-to-severe glaucoma from the early glaucoma [24].

They concluded that GC-IPL parameters can discriminate glaucoma suspects from healthy eyes and also all the consecutive stages of glaucoma from each other (from glaucoma suspect to moderate-to-severe glaucoma) [24].

In their study, Chen *et al*., in Taiwan, analyzed 67 eyes in each group, that is, preperimetric glaucoma (PPG) (67 patients) and controls (67 patients), measured their circumpapillary RNFL (cRNFL) thickness, mGCIPL thickness, and ONH limits using Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, California, USA). Absolute difference and ratios between mediocre hemisphere and larger hemisphere, IT and ST sectors, IT and SN sectors, IT and IN sectors, ST and IN sectors, as well as temporal and nasal sectors were calculated to express macular ganglion cell asymmetries. The asymmetry index was calculated as the absolute value of log10 of the ratio for each. The area under receiver working characteristics curve (AUROC), partial AUROC (pAUROC) ≥ specificities 90 and 95%, cut-off values, and sensitivities at specificities 90 and 95% were analyzed [25].

The largest AUROCs were found in IT GCIPL thickness (0.784), average RNFL thickness (0.767), and average C/D (0.746). log IT/SN index had the principal AUROC (0.734) amongst macular asymmetry parameters, followed by log IT/IN index (0.725) and absolute difference of IT-SN GCIPL thickness (0.715). Best measures of asymmetry (log IT/SN index) had comparable performance with persons of cRNFL, GCIPL, and ONH parameters (all $p>0.05$). Along with having the largest pAUROC based on the pAUROCs ≥90 and 95% specificity (0.044 and 0.019), IT/SN asymmetry index also had the highest analytic sensitivity at 90 and 95% specificities (52.2 and 46.3%) [25].

They concluded that GCIPL asymmetry measurements have diagnostic ability comparable to cRNFL, GCIPL, and ONH analysis for PPG and IT/SN asymmetry index is the best macular ganglion cell asymmetry parameter which could be a new parameter to detect early physical changes in PPG [25].

CONCLUSION

From this study, we may conclude that POAG causes considerable damage to the RGCs in the macula, in which when studied on SD-OCT

reveals a significant decrease in ganglion cell–inner plexiform thickness in inferior, inferotemporal, and supratemporal sectors of GCIPL SD-OCT scan.

The difference of thicknesses in GC-IPL layers of the macula of eyes with POAG and that of healthy eyes may aid in the discrimination of both the groups as a routine as well as in cases with abnormal appearances of the ONH.

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