Original Article

Comparison of spectral domain optical coherence tomography parameters between disc suspects and "pre-perimetric" glaucomatous discs classified on disc photos

Shruti Nitin Shah, Rathini Lilian David, Annadurai Parivadhini, Vijaya Lingam, Shantha Balekudaru, Ronnie Jacob George

Purpose: The aim of this study was to compare SD-OCT parameters between disc suspects and "pre-perimetric" glaucomatous discs classified on disc photos. **Methods:** Disc photos of suspicious discs with normal Humphrey visual fields (HVF) were graded as normal or pre-perimetric glaucomatous based on the consensus of three masked glaucoma specialists. RNFL and GCL-IPL maps of SD-OCT (Cirrus OCT) of these eyes were studied. Quantitative RNFL parameters were compared. Both groups were also compared with respect to parameters being classified as abnormal (at the 1% level), and the pattern of GCL-IPL and NFL maps were assessed qualitatively and classified as normal or pre-perimetric glaucomatous by a masked glaucoma specialist. **Results:** The average and inferior RNFL thicknesses were decreased in pre-perimetric glaucomatous eyes compared to normal eyes (p 0.01) The average, minimal, inferotemporal and inferior sector GCL-IPL thicknesses were decreased in pre-perimetric glaucomatous eyes (all $P < 0.002$) The highest AUC was for the inferior RNFL thickness (0.771) followed by average RNFL thickness (0.757) The sensitivity and specificity for any one abnormal RNFL parameter was 71.9% and 59.7%, for GCL-IPL parameters was 70% and 69.1% The positive (PLR) and negative likelihood ratios (NLR) were 1.78 and 0.47 for RNFL and 2.26 and 0.43 for GCL-IPL parameters. For the qualitative assessment of RNFL and GCL-IPL maps, the sensitivity, specificity, PLR and NLR were 75%, 77.2%, 3.29, and 0.32, respectively. **Conclusion:** Pre-perimetric disc suspects had greater OCT changes compared to normal disc suspects. Qualitative assessment of RNFL and GCL-IPL maps had the highest discriminatory ability.

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_1309_20

Quick Response Code:

Key words: Physiologic cups, pre-perimetric glaucoma, SD-OCT

Enlargement of the optic cup is a typical feature of glaucomatous optic nerve damage.[1] This cupping, which manifests in the form of increased vertical cup to disc diameter, could also be physiological. In some patients with glaucoma, standard automated achromatic perimetry does not detect visual fields defects until about 30-50% of retinal cell ganglions have been lost.[2,3] As a clinician, it is the suspicious disc with no visual field changes on standard achromatic perimetry, which poses a diagnostic dilemma. In spite of a good stereoscopic disc evaluation, it sometimes becomes difficult to differentiate between physiological and pathological cups. We often use imaging techniques to help differentiate these discs.

Optical coherence tomography (OCT) is one such imaging modality that enables to objectively measure the various parameters. The newer generation of spectral domain OCT (SD-OCT) have improved resolution, with increased sensitivity.[4,5] The role of OCT in diagnosis of glaucoma is well established.[6-13] There are studies which have proved the benefit of OCT in pre-perimetric glaucomas, as well.[14-17] Most of the studies used normal population as controls or had a distinct difference between the cases and controls. Having normal healthy subjects as controls could result in overestimating the diagnostic ability of a test. In real life, the test is used to help us in making a decision when dealing with suspicious discs. We report whether OCT, a test based on structural measurements, could help differentiate between pre-perimetric discs and functionally "normal" discs with an enlarged cup to disc ratio and to study the diagnostic ability of different OCT scanning protocols in detecting pre perimetric glaucoma.

Methods

This prospective observational study was conducted at a tertiary eye care hospital in South India. It was approved by the Institutional Review Board. The study adhered to the tenets of Declaration of Helsinki.

We identified eyes that had disc photos between 2011 and 2017. From these photos, eyes with suspicious optic discs defined as eyes with an increased vertical cup to disc ratio more than 0.7, neuroretinal rim thinning or notching, nerve fiber layer defects or disc hemorrhages were identified. Those eyes

Smt Jadhavabhai Nathamal Singhvee Glaucoma Services, Sankara Nethralaya, Chennai, Tamil Nadu, India

Correspondence to: Dr. Ronnie Jacob Geroge, Sankara Nethralaya (Main Campus), No. 41 (Old 18), College Road, Chennai - 600 006, Tamil Nadu, India. E-mail: drrg@snmail.org

Received: 04-May-2020 Revision: 18-Jun-2020
Accepted: 18-Aug-2020 Published: 17-Feb-2021

Cite this article as: Shah SN, David RL, Parivadhini A, Lingam V, Balekudaru S, George RJ. Comparison of spectral domain optical coherence tomography parameters between disc suspects and "pre-perimetric" glaucomatous discs classified on disc photos. Indian J Ophthalmol 2021;69:603-10.

whose visual fields were normal on clinical examination were included and their OCT parameters were evaluated.

Eyes with other conditions likely to affect the visual field or OCT results, for example, corneal opacity, neuro-ophthalmic or retinal disease were excluded. Eyes with definite glaucomatous visual field loss, that is, field defects in an area corresponding to glaucomatous damage and fulfilling all three Anderson's criteria, were also excluded from the study.

The patient demographic details, treatment details, best corrected visual acuity (BCVA), gonioscopy grading, intraocular pressure (IOP) were recorded.

Disc stereo photographs were taken using a fundus camera (FF450-plus with VISUPAC; Carl Zeiss Meditec). A non-simultaneous optic disc centered stereo disc image pair and red free RNFL photograph were taken for all participants.

The selected disc photographs were then graded by two masked glaucoma specialists (AP, RLD) as normal, borderline glaucomatous or glaucomatous. No definition of a glaucomatous disc was given, and the experts were asked to use their clinical expertise in classifying the disc. In the event of discrepancy of grading between the two clinicians, a third glaucoma specialist (RG) graded the disc. The final classification was always based on agreement of at least two examiners. In the event that none of the glaucoma specialists agreed individually on the disc grading, a consensus was reached upon. These graders performed their analysis masked from the results of SD-OCT and HVF tests or any other clinical data.

All SD-OCT scans were acquired with a Cirrus HD-OCT (software version 3.0.0.64) by using the Optic Disc Cube 200 x 200 protocol and macular cube 512 x 128 protocol. Only good-quality scans (quality score >6) were analyzed. Achromatic automated static perimetry with the central 24-2 SITA-standard protocol of Humphrey Field Analyzer 750 (Allergan Humphrey, San Leandro, CA) was done. Only discs with normal visual fields were included.

OCT images were classified in two ways: subjectively based on deviation maps and the TSNIT (temporal superior nasal inferior temporal) graph and objectively based on summary OCT parameter classification by the device.

One consultant (RG) classified the OCT scans into normal, only abnormal RNFL scan, only abnormal GCL-IPL (ganglion cell layer-inner plexiform layer) scan, both abnormal by assessing the thickness deviation maps and the TSNIT graph in case of the RNFL scan without access to the summary parameter values.

The summary parameter values were looked at separately. These included the disc parameters of disc area, rim area, average cup to disc ratio, vertical cup-to-disc ratio, cup volume, RNFL thickness measurements of four quadrants. From the macular cube, thickness in six sectors, minimum GCL-IPL thickness and average GCL-IPL thickness were used for analyses. The values flagged as statistically significant at 1% level were also analyzed separately.

The optic disc grading by the clinicians was used as the gold standard. For the purpose of statistical analysis the discs classified as borderline glaucomatous discs and glaucomatous were combined together as one group of pre-perimetric glaucomatous discs. The OCT parameters were compared between the two groups classified as normal and pre-perimetric glaucomatous on disc photos.

Statistical analyses

Continuous variables were assessed using the t test. Bonferroni correction was used for multiple measurements, wherever applicable. The Bonferroni corrected value was 0.0027 for quantitative parameters and 0.0031 for machine based OCT classification. An AUROC (area under receiver operating curve) was calculated for disease classification. The sensitivity, specificity, positive likelihood ratios (PLR) and negative likelihood ratios (NLR) were calculated using Medcalc (Med Calc Statistical software, version 8.1;Belgium) Analysis was performed using SPSS statistical software (version 14, SPSS Science Inc., Chicago, IL) and Medcalc.

Results

Eighty nine eyes of 50 patients with suspicious discs were included in the study. These were classified into 32 pre-perimetric glaucoma and 57 normal.

The mean age of the subjects was 44 ± 15 years with 63 males and 26 females. The visual acuity was 6/9 or better in all the eyes. The mean spherical refractive error was -1.79 ± 2.89 diopters (range -7.5 to + 7). The average intraocular pressure (IOP) in 89 eyes was 16 ± 3.04 mm hg; IOP of normal eyes was 16 ± 2.91 mm Hg and of pre-perimetric glaucomatous eyes was 14.97 ± 3.15 mm Hg ($P = 0.13$). Of these, 31 eyes were on topical anti glaucoma medications including 18 (31.58%) normal eyes and 13 (40.63%) pre-perimetric glaucomatous eyes ($P = 0.39$). On HVF, the mean deviation of pre-perimetric glaucomatous eyes was -3.05 ± 1.44 and of normal eyes was -2.3 ± 1.72 ($P = 0.03$). The pattern standard deviation (PSD) was also higher in pre-perimetric glaucomatous eyes than normal eyes but was not found to be statistically significant.

The OCT analysis of normal and pre-perimetric glaucomatous eyes showed statistical significant differences in a number of parameters. The average and inferior RNFL thicknesses, and inferotemporal, average and minimal GCL-IPL thickness were decreased in pre-perimetric glaucomatous eyes as compared to normal eyes [Table 1].

Areas under curves (AUC) were calculated for the ONH, RNFL and GCL-IPL parameters. The vertical CDR (0.64) and rim area (0.60) had highest AUC among the ONH parameters. The parameter with the highest sensitivity at 80% specificity was rim area. Among the RNFL parameters was inferior RNFL thickness (0.77) followed by the average RNFL thickness (0.76). The parameter with the highest sensitivity at 80% specificity was average RNFL thickness. On GCL-IPL analysis inferotemporal GCL-IPL thickness (0.75) and minimum GCL-IPL thickness (0.71) had the highest AUC. The parameter with the highest sensitivity at 80% specificity was inferotemporal thickness [Table 1].

The proportion of eyes with OCT values flagged as statistically significant at 1% level, that is, outside normal limits based on the normative database by the machine were also compared between both groups. A Bonferroni correction

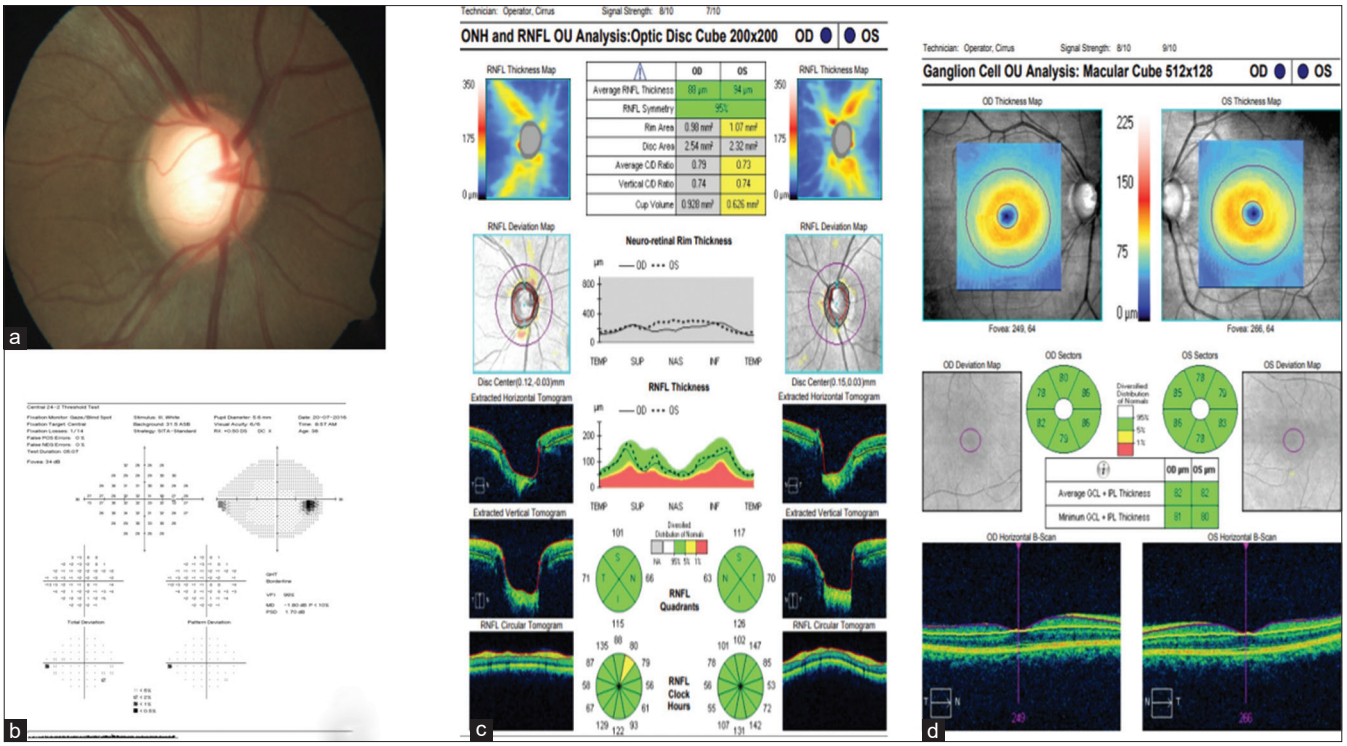

Figure 1: Disc photo (a) and HVF 24-2 perimetry (b) of a physiological large disc classified as normal; OCT shows no changes in both the RNFL (c) and GCL-IPL (d) maps

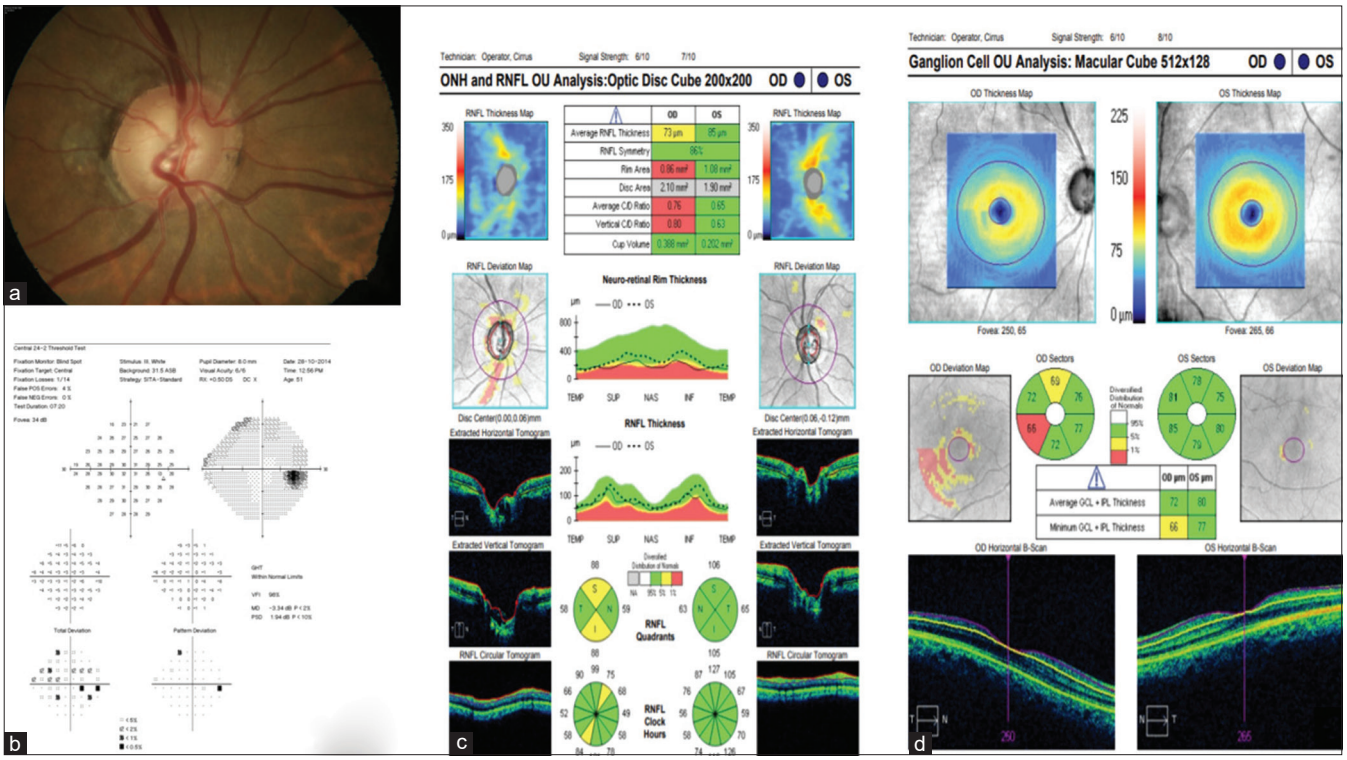

Figure 2: Disc photo (a) with HVF 24-2 perimetry (b) of a disc classified as pre-perimetric glaucomatous; OCT shows super-pixelated areas in wedge shaped pattern in RNFL deviation map with corresponding thinning seen in inferior quadrant and at 7 o clock position (c); the GCL-IPL map also shows thinning in the inferotemporal quadrant, the deviation map shows super-pixelated areas with a temporal raphe sign (d)

was applied here as well. The proportion of eyes with inferior RNFL thickness (59.38% pre-perimetric glaucoma, 21.05% normal) ($P < 0.0031$) flagged as being statistically significant at the 1% level were greater in pre-perimetric

Table 1: SD OCT parameters between the two groups and their diagnostic accuracy in discriminating between the two groups

Parameters	Normal	Pre-perimetric glaucoma	*P* value¶; AUROC	Sensitivity at 80% specificity
Rim area	0.89	0.84	0.17; 0.59 (0.46-0.73)	35.1
Disc area	2.57	2.49	0.49; 0.53 (0.40-0.66)	19.3
Average cup to disc ratio	0.81	0.81	0.95; 0.45 (0.31-0.59)	10.5
Vertical cup to disc ratio	0.77	0.79	0.09; 0.63 (0.51-0.76)	10.5
Cup volume	0.97	0.88	0.36; 0.53 (0.39-0.66)	22.8
Average RNFL thickness	80.93	72.84	**<0.0027**; 0.75 (0.64-0.86)	73.7
RNFL symmetry	83.84	80	0.11; 0.59 (0.47-0.71)	36.8
Superior RNFL thickness	102.49	92.19	0.003; 0.70 (0.58-0.81)	56.1
Nasal RNFL thickness	63.86	58.25	0.01; 0.67 (0.55-0.79)	36.8
Inferior RNFL thickness	100.02	87.25	**<0.0027**; 0.77 (0.66-0.87)	66.7
Temporal RNFL thickness	57.11	53.59	0.14; 0.60 (0.47-0.72)	26.3
Superonasal GCL-IPL thickness	78.31	73.87	0.009; 0.65 (0.52-0.78)	34.5
Superior GCL-IPL thickness	73.89	69.77	0.01; 0.67 (0.53-0.80)	38.2
Superotemporal GCL-IPL thickness	74.16	71	0.05; 0.65 (0.52-0.78)	37.7
Inferotemporal GCL-IPL thickness	76.18	69.83	**<0.0027**; 0.75 (0.64-0.86)	63.6
Inferior GCL-IPL thickness	73.31	68.43	0.003; 0.70 (0.58-0.82)	52.7
Inferonasal GCL-IPL thickness	76.25	71.93	0.02; 0.64 (0.51-0.76)	43.6
Average GCL-IPL thickness	75.2	70.57	**<0.0027**; 0.70 (0.58-0.82)	47.3
Minimal GCL-IPL thickness	71.75	66.03	**<0.0027**; 0.70 (0.58-0.82)	47.3

AUROC: Area under receiver operating curve; ONH: Optic nerve head; RNFL: Retinal nerve fiber layer; GCL-IPL: Ganglion cell layer-inner plexiform layer; ¶*P* value calculated using *t* test; Bonferroni value=0.0027

Table 2: Outside normal limits category on machine-based classification between the two groups

Parameters	Normal *n* (%)	Pre-perimetric glaucoma *n* (%)	*P* value*
Rim area	25 (43.9)	13 (41.9)	0.86
Vertical cup to disc ratio	19 (33.3)	13 (40.6)	0.33
Average RNFL thickness	9 (15.8)	16 (50)	0.01
RNFL symmetry	6 (10.5)	2 (6.3)	0.50
Superior RNFL thickness	11 (19.3)	13 (40.6)	0.05
Nasal RNFL thickness	3 (5.3)	2 (6.3)	0.85
Inferior RNFL thickness	12 (21.05)	19 (59.38)	**<0.0031**
Temporal RNFL thickness	4 (7)	5 (15.6)	0.20
Superonasal GCL-IPL thickness	5 (9.1)	8 (25)	0.03
Superior GCL-IPL thickness	9 (16.4)	15 (50)	0.01
Superotemporal GCL-IPL thickness	13 (23.6)	12 (40)	0.11
Inferotemporal GCL-IPL thickness	10 (18.2)	11 (36.7)	0.06
Inferior GCL-IPL thickness	12 (21.8)	16 (53.33)	**0.003**
Inferonasal GCL-IPL thickness	5 (9.1)	10 (33.3)	0.01
Average GCL-IPL thickness	9 (16.4)	17 (56.67)	**<0.0031**
Minimal GCL-IPL thickness	9 (15.8)	14 (46.7)	**0.002**
Any one parameter classified as outside normal limits on OCT	37 (64.9)	29 (90.6)	0.01
Any one ONH parameter classified as outside normal limits	27 (47.37)	14 (43.75)	0.69
Any one RNFL parameter classified as outside normal limits	23 (40.35)	23 (71.88)	0.004
Any one GCL-IPL parameter classified as outside normal limits	17 (29.82)	21 (65.63)	**0.001**

ONH: Optic nerve head; RNFL: Retinal nerve fiber layer; GCL-IPL: Ganglion cell layer-inner plexiform layer; **P* value calculated using χ^2; Bonferroni value=0.0031

glaucomatous eyes than normal eyes. Similarly, on GCL-IPL layer analysis, the superior (50% pre-perimetric glaucoma, 16.4% normal) ($P = 0.001$), inferior (53.33% pre-perimetric glaucoma, 21.8% normal) ($P = 0.003$), average GCL-IPL thickness (56.57% pre-perimetric glaucoma, 16.4% normal) ($P < 0.0031$) and minimum GCL-IPL layer thickness (46.7% pre-perimetric glaucoma, 15.8% normal) ($P = 0.002$) were classified as abnormal in a greater number of pre-perimetric glaucomatous eyes than

Table 3: Sensitivity, specificity and likelihood ratios (with 95% C.I.) of the normative database outside normal limits machine-based classification and clinical classification of the SDOCT parameters in discriminating between the two groups

Parameters	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio
Superior RNFL thickness	40.62 (23.7-59.36)	80.7 (68.09-89.95)	2.11 (1.07-4.14)	0.74 (0.54-1.01)
Inferior RNFL thickness	59.38 (40.64-76.30)	82.46 (70.09-91.25)	3.21 (1.69-6.08)	0.53 (0.35-0.80)
Nasal RNFL thickness	6.25 (0.77-20.81)	94.74 (85.38-98.9)	1.19 (0.21-6.74)	0.99 (0.89-1.1)
Temporal RNFL thickness	15.62 (5.28-32.79)	92.98 (83-98.05)	2.23 (0.64-7.71)	0.91 (0.77-1.07)
Average RNFL thickness	50 (31.89-68.11)	84.21 (72.13-92.52)	3.17 (1.58-6.33)	0.59 (0.41-0.85)
Inferotemporal GCL-IPL thickness	36.67 (19.93-56.14)	81.82 (69.10-90.92)	2.02 (0.97-4.19)	0.77 (0.57-1.04)
Inferior GCL-IPL thickness	53.33 (34.33-71.66)	78.18 (64.99-88.19)	2.44 (1.34-4.46)	0.6 (0.4-0.9)
Inferonasal GCL-IPL thickness	33.33 (17.29-52.81)	90.91 (80.05-96.98)	3.69 (1.38-9.74)	0.73 (0.56-0.96)
Superonasal GCL-IPL thickness	26.67 (12.28-45.89)	90.91 (80.05-96.98)	2.93 (1.05-8.18)	0.81 (0.64-1.02)
Superior GCL-IPL thickness	50 (31.3-68.7)	83.64 (71.2-92.23)	3.06 (1.52-6.13)	0.6 (0.41-0.87)
Superotemporal GCL-IPL thickness	22.22 (12.04-35.60)	58.06 (39.08-75.45)	1.69 (0.89-3.23)	0.79 (0.57-1.09)
Average GCL-IPL thickness	56.67 (37.43-74.54)	83.64 (71.2-92.23)	3.46 (1.76-6.8)	0.52 (0.34-0.79)
Minimal GCL-IPL thickness	46.67 (28.34-65.67)	83.64 (71.2-92.23)	2.96 (1.45-6.02)	0.64 (0.45-0.91)
Any one ONH parameter abnormal on machine-based classification	43.75 (26.36-62.34)	52.63 (38.97-66.02)	1.07 (0.72-1.58)	0.92 (0.57-1.49)
Any one RNFL parameter abnormal on machine-based classification	71.88 (53.25-86.25)	59.65 (45.82-72.44)	1.78 (1.2`-2.61)	0.47 (0.26-0.85)
Any one GCL-IPL parameter abnormal on machine-based classification	70 (50.6-85.27)	69.09 (55.19-80.86)	2.26 (1.43-3.59)	0.43 (0.24-0.77)
Any one parameter abnormal on machine-based classification	90.62 (74.98-98.02)	32.73 (20.68-46.71)	1.35 (1.09-1.67)	0.29 (0.09-0.9)
Clinical OCT abnormal	75 (56.6-88.54)	77.19 (64.14-87.26)	3.29 (1.96-5.52)	0.32 (0.17-6.60)
Clinical OCT and any one machine-based parameter abnormal	75 (56.6-88.54)	77.19 (64.14-87.26)	3.29 (1.96-5.52)	0.32 (0.17-6.60)
Clinical OCT or any one machine-based parameter abnormal	90.62 (74.98-98.02)	32.73 (20.68-46.71)	1.35 (1.09-1.67)	0.29 (0.09-0.9)

ONH: Optic nerve head; RNFL: Retinal nerve fiber layer; GCL IPL: Ganglion cell layer-inner plexiform layer

Table 4: Subjective clinical grading based on maps and combining clinical and machine based OCT classification between the two groups

Parameters	Normal *n*(%)	Pre-Perimetric Glaucoma *n*(%)	*P* value‖
Subjective clinical classification			
Normal	44(77.2)	8(25)	**<0.05**
Only RNFL deviation map abnormal	2(3.5)	5(15.6)	**0.04**
Only GCL-IPL deviation map abnormal	9(15.8)	8(25)	0.29
Both RNFL and GCL-IPL deviation maps abnormal	2(3.5)	11(34.4)	**<0.05**
Combining clinical and machine based OCT classification			
Only clinical OCT abnormal	13(22.8)	24(75)	**<0.05**
Clinical OCT or any one parameter classified as outside normal limits on machine OCT	37(64.91)	29(90.63)	**0.02**
Clinical OCT and any one parameter classified as outside normal limits on machine OCT	13(22.81)	24(75)	**<0.05**

ONH: Optic nerve head, RNFL: Retinal nerve fiber layer, GCL-IPL: Ganglion cell layer-inner plexiform layer, ‖P value calculated using $\chi 2$ test

normal eyes. Any one RNFL parameter was abnormal in 71.88% and 40.35% of eyes classified as pre-perimetric glaucomatous and normal, respectively ($P = 0.004$). Any one GCL-IPL parameter was abnormal in 65.63% of pre-perimetric glaucomatous and 29.82% of normal eyes ($P = 0.001$). For ONH scans the proportion of eyes with any one parameter classified as outside normal limits was not significantly different between the two groups (47.37% in normal eyes and 43.75% in pre-perimetric glaucomatous eyes) ($P = 0.69$). Any one parameter (RNFL/GCL-IPL or ONH) classified as abnormal by the OCT was present in 90.6% eyes classified as pre-perimetric glaucomatous and 64.9% eyes classified as normal ($P = 0.014$) [OR = 10.1 (3.6-27.9)] [Table 2].

Table 3 shows the sensitivity, specificity and likelihood ratios of parameters based on the normative database classification.

Table 5: Raw data values between the two groups after clinical OCT classification based on maps

	Normal	Pre-perimetric glaucoma	*P* value**
Rim area	0.92	0.80	**0.001**
Disc area	2.61	2.44	0.119
Average CDR	0.80	0.81	0.214
Vertical CDR	0.77	0.79	0.014
Cup volume	0.92	0.96	0.737
Average RNFL thickness	82.37	71.92	**<0.0026**
Rnfl symmetry	84.02	80.27	0.117
Superior RNFL thickness	103.38	89.62	**<0.0026**
Nasal RNFL thickness	64.00	58.81	0.018
Inferior RNFL thickness	101.25	87.16	**<0.0026**
Temporal RNFL thickness	58.88	51.57	0.001
Superonasal GCL-IPL thickness	79.94	72.17	**<0.0026**
Superior GCL-IPL thickness	76.40	66.77	**<0.0026**
Superotemporal GCL-IPL thickness	76.38	68.29	**<0.0026**
Inferotemporal GCL-IPL thickness	77.94	68.51	**<0.0026**
Inferior GCL-IPL thickness	75.20	66.43	**<0.0026**
Inferonasal GCL-IPL thickness	77.94	69.86	**<0.0026**
Average GCL-IPL thickness	77.02	68.77	**<0.0026**
Minimum GCL-IPL thickness	74.16	63.26	**<0.0026**

ONH: Optic nerve head; RNFL: Retinal nerve fiber layer; GCL IPL: Ganglion cell layer-inner plexiform layer; ***P* value calculated using t test; Bonferroni value=0.0026

The sensitivity and specificity if even one parameter was flagged as abnormal on ONH analysis was 43.75% and 52.63%, respectively. For RNFL analysis it was 71.88% and 59.65%, respectively. On GCL-IPL analysis, the sensitivity and specificity if even one parameter was abnormal was 70% and 69.09%, respectively. The sensitivity, specificity when only one parameter was found to be abnormal was 90.62% (74.98–98.02) (95% C.I) and 32.73 (20.68–46.71)(95% C.I.).

On clinical grading of OCT report based on deviation from normal maps, 22.8% of normal eyes and 75% of pre-perimetric glaucomatous eyes were classified as abnormal. Also, only the retinal nerve fiber layer, only the ganglion cell layer and both the layers were classified as abnormal in 3.5%, 15.8% and 3.5% in normal eyes and 15.6%, 25% and 34.4% in pre-perimetric glaucomatous eyes, respectively [Table 4]. On combining abnormal GCL-IPL layer only, abnormal RNFL layer only or both abnormal as one broad category of abnormal, 22.8% of normal eyes and 75% of pre-perimetric glaucomatous eyes were classified as abnormal ($P < 0.05$). The sensitivity and specificity of using this form of classification was 75% (56.6%–88.54%) and 77.19% (64.14%–87. 26%) and the positive and negative likelihood ratio were 3.29 (1.96–5.52) and 0.32 (0.17–6.6), respectively [Table 3].

When we compared summary parameters between these two groups both average, superior, inferior and temporal RNFL and all GCL-IPL thicknesses were lower in pre-perimetric glaucomatous eyes than normal eyes. Among the ONH parameters only the rim area was found to be less in pre-perimetric glaucomatous eyes than normal eyes [Table 5].

We assessed the combination of the clinical classification and the normative database classification. When either a single OCT value was flagged as abnormal or clinical OCT classified as abnormal were considered, 90.63% pre-perimetric glaucomatous eyes and 64.91% normal eyes were abnormal [Table 4]. The sensitivity and specificity were 90.62% (74.98–98.02) and 32.73 (20.68–46.71).

When both were combined, 22.81% of normal eyes and 75% of pre-perimetric glaucomatous eyes were found to be abnormal ($P < 0.05$) [Table 4]. The sensitivity and specificity on combining both the clinical OCT and the normative database classification was 75% (56.6%–88.54%) and 77.19% (64.14%–87. 26%)

Discussion

In this study we evaluated the OCT features of disc suspects classified as normal or pre-perimetric glaucomatous by glaucoma specialists. We studied the raw data values, the outside normal limits normative database classification and the deviation from normal thickness map provided by the machine of the RNFL and GCL-IPL maps.

In our study, we found that based on raw data values, the groups differed in the average and inferior RNFL thickness along with inferotemporal, inferior, average and minimal GCL-IPL thickness. The disc areas between the two groups were comparable and the eyes classified as normal had a larger disc area compared to the ones classified as having pre-perimetric glaucoma. Thus, the classification was done on the basis of neuroretinal rim and nerve fiber layer features and not on vertical cup to disc area which tends to happen with large discs.

When we analyzed the AUROC of all the OCT parameters, the AUROC were better for RNFL and GCL-IPL parameters than the disc parameters. These results are similar to other studies done for pre-perimetric glaucomas.[18] The possible reason

could be that in pre perimetric glaucoma, disc changes appear late and thus there is not much differentiation provided by the machine based on the disc features. The AUROC was highest for the average (0.76) and inferior (0.78) RNFL parameters. A meta-analysis of OCT use in pre perimetric glaucoma found that AUROC was highest for average RNFL (0.831) and inferior RNFL (0.828) parameters.[18]

We also evaluated the likelihood ratios (LRs) associated with the outside normal limit diagnostic categorization of the SD-OCT. A LR of more than one argues for the diagnosis of interest.[19] The closer the value to zero, less likely is the disease. Our LRs for outside normal limit ranged from 1.12 to 3.69 Thus, the magnitude of LRs provided by our study had a mild effect on the post-test probability. A similar study conducted by Rao *et al*., found moderate effects on the post-test probability.[16] In their study cases were eyes with early glaucoma and controls were disc suspects, ruled out as normal by glaucoma experts but with physiological variations in the optic disc. Whereas in our study, the entire study population consisted of disc suspects who were perimetrically normal and these were then classified by the experts as normal or pre perimetric discs. One more study by Rao and colleagues had disc suspects as the entire study population which they too classified as normal and pre perimetric discs.[20] Their likelihood ratios were better than ours, showing a moderate effect on post-test probability. A possible reason could be that in their control group of pre-perimetric discs the fellow eye with perimetric glaucoma. Thus their pre perimetric discs could have had more morphological clues. In our study, not all pre-perimetric discs had fellow eyes with perimetric glaucoma. Another study by Lisboa *et al.* followed disc suspects longitudinally over a period of 15 years.[17] At the end of 15 years, the eyes which showed disc changes were classified as pre perimetric and the ones which did not show any change were classified as normal. The likelihood ratios obtained by them had a large impact on the post-test probability. A reason for this could be that they were comparing disc suspects who showed changes over a period of 15 years with disc suspects who did not who were probably essentially normal eyes, whereas our study had all eyes as disc suspects, who could potentially progress.

In our study, the deviation from normal thickness map showed good diagnostic ability, especially the RNFL map. Comparison of the GCL-IPL thickness deviation maps was not able to differentiate normal and pre-perimetric glaucomatous eyes. Kang *et al.* studied the RNFL deviation from normal thickness maps and found it to be better than the normative database classification.[21] They excluded isolated islands depicted as abnormal and similar to our method required wedge shaped defects to reach the disc margin [Figs. 1 and 2]. Another study done by Leung *et al.* also showed that the thickness from normal deviation map provides more morphological and spatial information.[22] Both the studies had normal eyes with no features suspicious of glaucoma as the control groups. This explains the high AUROC values obtained in their study. The reason why the thickness from normal deviation map fares better than the normative database classification is that a cluster of points in the normative database classification are averaged the average is taken into consideration, this could lead to missing of small defects, which can be detected by looking at the deviation from normal thickness map.

The GCL-IPL thickness from normal deviation map was studied by Sung *et al*. in patients with pre perimetric glaucoma.[23] They found that the mGCIPL thickness deviation map showed good diagnostic ability in pre perimetric glaucoma and found it comparable to the pRNFL thickness deviation map, whereas it was not the same in our case. They considered all points showing superpixelated areas as red as abnormal, whereas we gave more importance to the presence of a hemi meridian defect and involvement of points closer to the fovea [Fig. 2]. We used clinical judgement of defect pattern to classify the thickness from normal deviation map as normal or pre-perimetric glaucomatous.

When clinicians looked at the OCT subjectively, eyes classified as abnormal were fairly low, but machine based classification showed more eyes as abnormal. This is probably because clinicians look at the pattern of defects, as well, when making a decision.

On combining the thickness deviation maps and outside normal limits categorization, we found a PLR of 3.29. When either the clinical OCT or any parameter outside limit was considered, the NLR was 0.29. This roughly translates as follows, that is, when both parameters are abnormal, the likelihood of the disease increases by 20% and when either of the parameters is not abnormal the likelihood of the disease decreases by 25%. Thus, for a clinician who considers that a suspicious disc has a pre-test probability of 40% of being glaucomatous, our findings suggest that OCT can increase the post-test probability to 69% and with a pre-test probability of 60%, the post-test probability increases to 83%. Conversely, because of its NLR of 0.29 post-test probabilities would decrease to 19% and 30% with pre-test probabilities of 40%–60%. Considering that these discs were considered pre-perimetric glaucomatous by a consensus from three glaucoma specialists this degree of change in probability would be enough to rule in or rule out disease.

The strength of our study is that by including all suspicious discs as the study population we tried to simulate a real life situation. We also took into consideration the deviation from normal maps while classifying the OCT as normal or abnormal.

Our limitation is that our interpretation is based on a one time single test. We had a few patients with spherical power exceeding ± five diopters. However, they were few in number and would not impact the result to a large extent.

Conclusion

In conclusion, spectral domain OCT does have a role in pre-perimetric glaucoma. The different scanning protocols should be looked at carefully, and clinical judgement should be used when interpreting results.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Jonas JB, Zäch FM, Gusek GC, Naumann GO. Pseudoglaucomatous physiologic large cups. Am J Ophthalmol 1989;107:137-44.
2. Quigley HA, Addicks EM, Green WR. Optic nerve damage in

human glaucoma: III Quantitative correlation of nerve fiber loss and visual field defect in glaucoma, ischemic neuropathy, papilledema, and toxic neuropathy. Arch Ophthalmol 1982;100:135-46.

3. Mikelberg FS, Yidegiligne HM, Schulzer M. Optic nerve axon count and axon diameter in patients with ocular hypertension and normal visual fields. Ophthalmology 1995;102:342-8.
4. Nassif N, Cense B, Park B, Pierce M, Yun S, Bouma B, *et al*. *In vivo* high-resolution video-rate spectral-domain optical coherence tomography of the human retina and optic nerve. Opt Express 2004;12:367-76.
5. Wojtkowski M, Srinivasan V, Ko T, Fujimoto J, Kowalczyk A, Duker J. Ultrahigh-resolution, high-speed, Fourier domain optical coherence tomography and methods for dispersion compensation. Opt Express 2004;12:2404-22.
6. Zangwill LM, Bowd C, Berry CC, Williams J, Blumenthal EZ, Sánchez-Galeana CA, *et al*. Discriminating between normal and glaucomatous eyes using the Heidelberg retina tomograph, GDx nerve fiber analyzer, and optical coherence tomograph. Arch Ophthalmol 2001;119:985-93.
7. Naithani P, Sihota R, Sony P, Dada T, Gupta V, Kondal D, *et al*. Evaluation of optical coherence tomography and heidelberg retinal tomography parameters in detecting early and moderate glaucoma. Invest Ophthalmol Vis Sci 2007;48:3138-45.
8. Medeiros FA, Zangwill LM, Bowd C, Vessani RM, Susanna R Jr, Weinreb RN. Evaluation of retinal nerve fiber layer, optic nerve head, and macular thickness measurements for glaucoma detection using optical coherence tomography. Am J Ophthalmol 2005;139:44-55.
9. Park SB, Sung KR, Kang SY, Kim KR, Kook MS. Comparison of glaucoma diagnostic capabilities of Cirrus HD and Stratus optical coherence tomography. Arch Ophthalmol 2009;127:1603-9.
10. Parikh RS, Parikh S, Sekhar GC, Kumar RS, Prabakaran S, Babu JG, *et al*. Diagnostic capability of optical coherence tomography (Stratus OCT 3) in early glaucoma. Ophthalmology 2007;114:2238-43.
11. Leung CK, Cheung CY, Weinreb RN, Qiu Q, Liu S, Li H, *et al*. Retinal nerve fiber layer imaging with spectral-domain optical coherence tomography: A variability and diagnostic performance study. Ophthalmology 2009;116:1257-63.
12. Rao HL, Zangwill LM, Weinreb RN, Sample PA, Alencar LM, Medeiros FA. Comparison of different spectral domain optical coherence tomography scanning areas for glaucoma diagnosis. Ophthalmology 2010;117:1692-9.
13. Leite MT, Rao HL, Zangwill LM, Weinreb RN, Medeiros FA. Comparison of the diagnostic accuracies of the Spectralis, Cirrus, and RTVue optical coherence tomography devices in glaucoma. Ophthalmology 2011;118:1334-9.
14. Begum VU, Addepalli UK, Yadav RK, Shankar K, Senthil S, Garudadri CS, *et al*. Ganglion cell-inner plexiform layer thickness of high definition optical coherence tomography in perimetric and preperimetric glaucoma. Invest Ophthalmol Vis Sci 2014;55:4768-75.
15. Blumberg DM, De Moraes CG, Liebmann JM, Garg R, Chen C, Theventhiran A, *et al*. Technology and the glaucoma suspect. Invest Ophthalmol Vis Sci 2016;57:80-5.
16. Rao HL, Kumbar T, Addepalli UK, Bharti N, Senthil S, Choudhari NS, *et al*. Effect of spectrum bias on the diagnostic accuracy of spectral-domain optical coherence tomography in glaucoma. Invest Ophthalmol Vis Sci 2012;53:1058-65.
17. Lisboa R, Leite MT, Zangwill LM, Tafreshi A, Weinreb RN, Medeiros FA. Diagnosing preperimetric glaucoma with spectral domain optical coherence tomography. Ophthalmology 2012;119:2261-9.
18. Kansal V, Armstrong JJ, Pintwala R, Hutnik C. Optical coherence tomography for glaucoma diagnosis: An evidence based meta-analysis. PLoS One 2018;13:e0190621.
19. McGee S. Simplifying likelihood ratios. J Gen Intern Med 2002;17:646-9.
20. Rao HL, Addepalli UK, Chaudhary S, Kumbar T, Senthil S, Choudhari NS, *et al*. Ability of different scanning protocols of spectral domain optical coherence tomography to diagnose preperimetric glaucoma. Invest Ophthalmol Vis Sci 2013;54:3417-25.
21. Kang SY, Sung KR, Na JH, Choi EH, Cho JW, Cheon MH, *et al*. Comparison between deviation map algorithm and peripapillary retinal nerve fiber layer measurements using Cirrus HD-OCT in the detection of localized glaucomatous visual field defects. J Glaucoma 2012;21:372-8.
22. Leung CK, Lam S, Weinreb RN, Liu S, Ye C, Liu L, *et al*. Retinal nerve fiber layer imaging with spectral-domain optical coherence tomography: Analysis of the retinal nerve fiber layer map for glaucoma detection. Ophthalmology 2010;117:1684-91.
23. Sung MS, Yoon JH, Park SW. Diagnostic validity of macular ganglion cell-inner plexiform layer thickness deviation map algorithm using cirrus HD-OCT in preperimetric and early glaucoma. J Glaucoma 2014;23:144-51.