EXTENDED REPORT

Peripapillary fundus perimetry in eyes with glaucoma

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Aims: To evaluate, with fundus perimetry, the peripapillary differential light threshold (DLT) in eyes with glaucoma and ocular hypertension (OHT), and compare it with peripapillary retinal nerve fibre layer (RNFL) thickness.

Methods: 35 glaucomatous, 29 OHT and 24 control eyes were included. Peripapillary DLT at 1° from the optic nerve head was quantified with fundus perimetry; peripapillary RNFL thickness was measured over the same area by optical coherence tomography.

Results: Mean (SD) peripapillary DLT was 19.2 (1.7), 17.6 (4.2) and 10.1 (6.9) dB in control, OHT and glaucomatous eyes, respectively ($p < 0.001$). Mean (SD) RNFL thickness was 98.4 (35.3), 83.9 (35.1) and 55.8 (28.2) μm, respectively ($p < 0.001$). Mean peripapillary DLT showed higher sensitivity and specificity in differentiating the three groups compared with RNFL thickness.

Conclusion: Progressive, significant reduction of peripapillary DLT was documented in OHT and glaucomatous eyes compared with controls ($p < 0.001$). DLT reduction parallels RNFL reduction.

G laucoma is an optic neuropathy characterised by a specific and progressive injury to the optic nerve head (ONH) and retinal nerve fibre layer (RNFL), resulting in progressive loss of vision.[1] Early detection and prevention of RNFL glaucomatous damage is mandatory, because injury to the RNFL is largely irreversible.[2 3] The diagnosis of glaucoma is based on the appearance of the ONH and standard achromatic automated perimetry, but damage to the RNFL has been shown to precede visual field loss.[1–4] It has been shown that 30–50% of retinal ganglion cells may be lost before an abnormality appears on standard automated perimetry.[4 5] Therefore, morphological and functional evaluation of RNFL is essential in detecting and monitoring glaucoma.[6 7] ONH and RNFL morphometry is carried out using different approaches, mainly optical coherence tomography.[7–11] Many different functional tests (short-wavelength automated perimetry, frequency-doubling technology perimetry) have also been proposed with controversial results.[12 13] Fundus perimetry, or microperimetry, is a functional test that quantifies differential light threshold (DLT) at selected areas, chosen by the examiner, under real-time fundus control.[14 15] Fundus perimetry data are independent of eye movements, and exactly related to the stimulated areas.[16] The aim of this study was to evaluate whether peripapillary fundus perimetry is modified in eyes with glaucoma and ocular hypertension (OHT), and to compare the functional data and morphological information obtained by peripapillary optical coherence tomography (OCT).

MATERIALS AND METHODS

Subjects

A total of 88 eyes of 88 Caucasian adults were studied: 35 were affected by glaucoma and 29 by OHT; 24 healthy eyes were used as controls. Patients affected by glaucoma and ocular hypertension were consecutively recruited from our glaucoma service. No patients declined to be included.

All subjects had a negative history for systemic diseases. All eyes underwent a full ophthalmological examination including visual acuity, intraocular pressure (IOP) measurement with a Goldmann tonometer (HAAG-STREIT AG, Köniz, Switzerland), corneal pachymetry to confirm IOP values and dilated stereoscopic fundus examination of ONH. All eyes had a best-corrected visual acuity of at least 20/40. Patients with retinal diseases or previous retinal surgery were excluded. Standard visual field testing was obtained using static automated perimetry carried out by the Swedish Interactive Thresholding Algorithm Standard 24-2 perimetry (Carl Zeiss Meditec, Jena, Germany). A visual field was defined as reliable when fixation losses were <20%, and false-positive and false-negative rates were <25%.

Controls had a negative family history for glaucoma, IOP ≤21 mm Hg, normal ONH and normal visual field. OHT eyes were defined as having IOP≥21 mm Hg, normal visual field and normal ONH as proposed by the Ocular Hypertension Treatment Study.[17] Glaucomatous eyes had loss or thinning of the neuroretinal rim, notching or escavation, with an associated visual field defect in the corresponding location. A glaucomatous visual field defect had ≥3 significant ($p < 0.05$) non-edge contiguous points with at least one point at the $p < 0.01$ level at the same side of the horizontal meridian in the pattern deviation plot, and graded outside normal limits in the glaucoma hemifield test.[18] This study was approved by the institutional review board of the University of Padova, Padova, Italy.

OCT measurements

Optical coherence tomography was carried out with OCT 3 (STRATUS OCT, Carl Zeiss, Jena, Germany). The optical principles and applications of OCT have been recently reviewed by Jaffe and Caprioli.[19] Each subject underwent the Fast RNFL thickness (3.4) scan protocol. The measurements were aligned on the basis of the right eye orientation. The superior clock hour was 1 o'clock and the other 11 were assigned accordingly clockwise in the right eye and anticlockwise in the left eye.

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Fundus perimetry

Fundus perimetry was carried out in all patients using an automatic fundus perimeter (MP1 Microperimeter, Nidek Technologies, Padova, Italy). Fundus is imaged in real time on a video monitor using an infrared fundus camera.[14] Fixation target and stimuli are projected on a liquid crystal colour monitor completely controlled by software designed for the purpose. Background illumination is set at 4 apostilb (asb). Stimulus intensity may be varied on one (0.1 log) step scale from 0 to 20 dB, where 0 dB represents the brightest luminance of 400 abs (127 cd/m^2). The following parameters were used: background at 4 asb, stimulus size Goldmann III, 4-2-1 double staircase strategy, standardised peripapillary grid and a cross of 1° as fixation target.

The peripapillary grid is composed of a ring of 12 stimuli exactly located at 1° from the ONH, corresponding to the location of the standard OCT scan. The stimuli are positioned along 12 rays aligned on the basis of the right eye orientation. The superior clock hour is 1 o'clock, and the others are assigned accordingly clockwise in the right eye and anticlockwise in the left eye (fig 1). An automatic eye tracker compensates for eye movements.[14 15] This allows correct matching between expected stimulus position on the retina and actual projection position. Light stimuli are randomly presented during the examination, and results are reported in decibels. To ensure a better clinical correlation between fundus perimetry and fundus abnormalities, functional results are displayed on a colour digital retinograph acquired with a charge-coupled device colour camera.

Statistical analysis

The means of DLT (dB) and RNFL thickness (μm) in the three groups (glaucoma, OHT and controls) were compared by two-way analysis of variance for repeated measures (group per retinal sector), where group was considered the between factor and retinal sector the within factor. Scheffe's test was used for retrospective multiple comparisons. Receiver operating characteristic (ROC) curves were traced
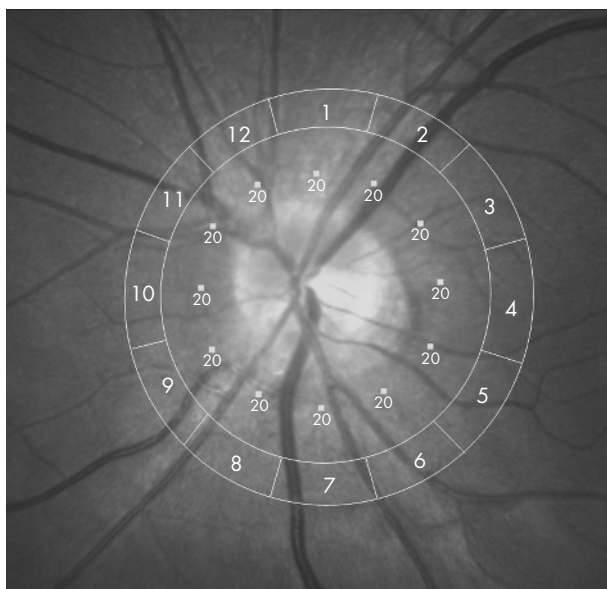

Figure 1 Peripapillary fundus perimetry grid. The ring of 12 stimuli is located 1° from the ocular hypertension border. Numbers refer to the retinal sector orientation for fundus perimetry and optical coherence tomography data. The clock hour measurements are aligned on the basis of right orientation; 1 o'clock corresponds to the superior region, 4 o'clock to the nasal region, 7 o'clock to the inferior region and 10 O'clock to the temporal region for both right and left eyes.

for both instruments to assess their capability to differentiate OHT or glaucomatous eyes from normal eyes. In addition, the area under the ROC curve (AROC) was calculated to describe the ability of each retinal sector to differentiate OHT and glaucomatous eyes from normal eyes. The best combination of sensitivity and specificity in each retinal sector was quantified. In all statistical analyses, p<0.05 was considered significant. Statistical analyses were carried out using SAS V.8.2. Med Calc V.8.2.1.0 was used to analyse ROC curves and to compare AROC.

RESULTS

In all, 24 controls (10 men, 14 women; mean SD age 60.1 (10.7) years), 29 OHT eyes (15 men, 14 women; mean (SD) age 60.7 (11.2) years) and 35 glaucomatous eyes (11 men, 24 women; mean (SD) age 63.0 (9.1) years) were evaluated (table 1).

The mean (SD) value of peripapillary fundus perimetry (DLT) was 19.2 (1.7) dB in controls, 17.6 (4.2) dB in OHT eyes and 10.1 (6.9) dB in glaucomatous eyes, respectively. The mean (SD) value of RNFL thickness was 98.4 (35.3) μm in controls, 83.9 (35.1) μm in OHT eyes and 55.8 (28.2) μm in glaucomatous eyes.

Figure 2 shows the peripapillary DLT profile (functional profile) by retinal sector and group of patients (table 2). The functional profile of normal eyes is markedly regular, whereas that in OHT and glaucomatous eyes shows a double-hump pattern with troughs at sectors 1 (superior sector) and 7 (inferior sector) in the OHT group, and at sectors 12 and 7 in the glaucoma group. Figure 3 shows the RNFL profile (morphological profile) by retinal sector and group of patients (table 3). The morphological profile in all three groups shows a double-hump pattern with peaks at sectors 7 (inferior sector) and 12 (superotemporal sector), and troughs at sectors 3 (nasal sector) and 10 (temporal sector).

At OCT analysis, significant differences in all retinal sectors (p<0.001) between normal and OHT versus glaucomatous eyes were found, whereas those between normal versus OHT eyes were significant only in sectors 2–4, 7–9, and 11 (p<0.001). The peripapillary fundus perimetry data analysis showed progressive, significant reduction of peripapillary sensitivity in all retinal sectors in glaucomatous eyes (p<0.001) and in sectors 1, 7 and 12 in OHT eyes (p<0.001) versus control eyes.

Peripapillary fundus perimetry combination of sensitivity and specificity for each retinal sector shows a sensitivity between 71.4% and 94.3% for a specificity ≥75% in normal versus glaucomatous eyes (table 4). In normal versus OHT eyes, we found the best combination of sensitivity and specificity in sectors 1, 7 and 12, with a sensitivity between 58.6% and 65.5% for a specificity between 79.2% and 100% (table 5). The OCT best combination of sensitivity and specificity for each retinal sector shows a sensitivity between 66.7% and 97.0% for a specificity between 62.5% and 95.8% for normal versus glaucomatous eyes (table 4). The OCT best trade-off between sensitivity and specificity for each retinal sector shows a sensitivity between 48.3% and 89.7% for a specificity between 45.8% and 91.7% for normal versus OHT eyes (table 5).

The average of 12 OCT measures shows a sensitivity of 90.9% for a specificity of 100% in normal versus glaucomatous eyes. The same average in normal versus OHT eyes shows a sensitivity of 72.4% for a specificity of 79.2%. Peripapillary fundus perimetry average of 12 measures of best trade-off between sensitivity and specificity shows a sensitivity of 94.3% for a specificity of 95.8% in normal versus glaucomatous eyes, and a sensitivity of 79.3% for a specificity of 79.2% in normal versus OHT eyes.

Table 1 Characteristics of study population:

	Normal	OHT	Glaucoma	p Value
No of subjects	24	29	35	
Age (years)	60.1 (10.7)	60.7 (11.2)	63.0 (9.1)	0.508*
Male/female)	10/14	15/14	11/24	0.258†
Visual field mean deviation(dB)	−0.48 (0.90)	−0.63 (1.2)	−3.5 (1.7)	<0.001*
Visual field PSD (dB)	0.82 (0.65)	1.12 (0.88)	5.9 (4.7)	<0.001*

Values are mean (SD). OHT, ocular hypertension; PSD, pattern standard deviation.
*Analysis of variance; †χ^2 test.

DISCUSSION

Numerous studies have shown that the RNFL becomes progressively atrophic in glaucoma.[20–22] Damage to the RNFL and after ONH frequently precedes visual field loss.[1–4] Modern imaging devices are non-invasive techniques aimed at evaluating morphological changes in ONH and RNFL.[6–11] On the other hand, the gold standard for detecting the functional effect of glaucoma on neuronal damage remains the standard visual field examination.[10–13 23]

According to current literature, the most reproducible and reliable morphological parameter for analysing peripapillary areas seems to be the quantification of peripapillary RNFL thickness carried out by OCT.[24–29] Kanamori et al[24] showed that OCT has the ability to detect early glaucomatous changes by measuring peripapillary RNFL thickness, particularly in the inferior quadrant. Zangwill et al[25] and Soliman et al[26] reported a marked relationship between the mean deviation of visual field and the peripapillary RNFL thickness, except in the nasal area. Parisi et al[27] showed a correlation between electroretinography pattern and temporal RNFL thickness, and El Beltagi et al[28] found a correlation between localised RNFL thinning measured by OCT and localised visual field defects. OCT measurement of the peripapillary RNFL thickness seems to discriminate between eyes with glaucoma and controls, but it seems less sensitive for OHT.[29] Pattern electroretinography has recently beenclaimed to predict the development or progression of glaucomatous disease.[30]

Considerable retinal ganglion cell loss has been shown to occur in the macula in primate experimental glaucoma. It has also been shown that because of the redundancy of ganglion cells in the macula, greater loss of ganglion cells is required in the central compared with the peripheral retina for equal effects on visual sensitivity.[31–34] Moreover, as all nerve fibres radiate towards the ONH, circular analysis around the ONH may be able to detect damage in areas that are not included in the macular analysis (the nasal aspect of ONH).[34] Orzalesi et al,[35] Miglior[36] and Rohrschneider et al[37] previously pointed to the importance of SLO fundus perimetry (peripapillary and extrapapillary) in glaucomatous eyes to detect early loss of retinal sensitivity. Rohrschneider suggested that analysing peripapillary DLT may show morphological changes that precede typical visual field defects.[37] Okada et al[38] showed that SLO fundus perimetry may be an alternative method of evaluating advanced glaucoma. Unfortunately, the data about fundus perimetry in glaucomatous eyes were never replicated because the SLO microperimetry technique limited further studies.[16 39] Fundus perimetry was developed as a functional clinical application of scanning laser ophthalmoscope.[39–42] Recently, a reliable and simple automatic fundus perimeter was introduced in clinical practice.[14 15] The MP1 microperimeter and Humphrey perimeter use non-comparable protocols, mainly because of different background intensity (4 v 31.5 asb, respectively) and control of stimulus projection. This control is fully reliable in fundus perimetry, where an active eye tracking is used.

Our data confirm the progressive and specific reduction in thickness of peripapillary RNFL with progressive glaucomatous damage (normal v OHT v glaucoma) documented by peripapillary OCT.[18 19] Our data also document the loss of peripapillary DLT quantified with peripapillary fundus perimetry in the same eyes. Using both techniques, we found that in all peripapillary-examined sectors, glaucomatous eyes showed lower morphological and functional values (p<0.05). At OCT analysis in OHT eyes, sectors 2–4, 7–9 and 11 had mean values significantly lower than normal ones (p<0.05). Peripapillary fundus perimetry data showed that the differences between normal and OHT eyes were significant (p<0.05) in sectors 1, 7 and 12. A better ability of fundus perimetry to discriminate OHT from normal eyes in retinal sectors 1 (superior region), 7 (inferior region) and 12 (superotemporal region) is confirmed by higher values of AROC data (table 5). Fundus perimetry documents glaucomatous damage beginning over the inferior and superior arcuate fibres, where OCT shows a thinning of the RNFL.

Our data show that peripapillary fundus perimetry is able to detect and topographically document early functional RNFL glaucomatous changes through exact quantification of
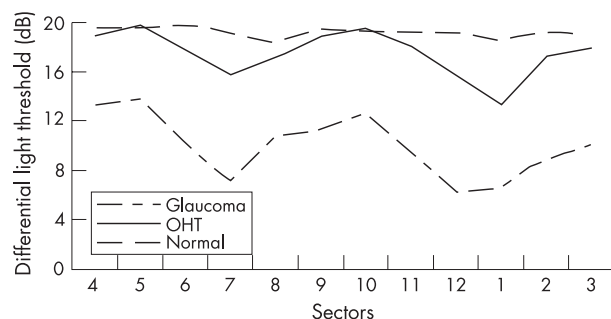

Figure 2 Peripapillary differential light threshold profile comparing normal, ocular hypertension (OHT) and glaucomatous eyes. The average peripapillary differential light threshold was calculated in each sector and compared among the diagnostic groups with analysis of variance ($F_{22,814}=3.06$, p<0.001). Sector orientation is reported in the legend of fig 1.
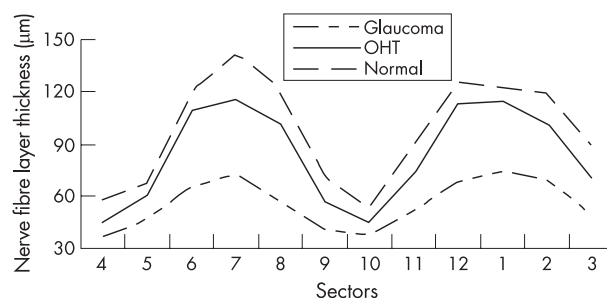

Figure 3 Peripapillary nerve fibre layer thickness profile comparing normal, ocular hypertension (OHT) and glaucomatous eyes. The average nerve fibre layer thickness was calculated in each sector and compared among the diagnostic groups using analysis of variance ($F_{22,913}=9.74$, p<0.001). Sector orientation is reported in the legend of fig 1.

Table 2 Peripapillary differential light threshold (mean (SD) (95% CI) for each of the 12 sectors at 1° from the optic nerve head as quantified by fundus perimetry

Retinal sector*	Glaucoma	OHT	Control
1	6.7 (5.6) (4.7 to 8.7)	13.3 (5.9) (10.9 to 15.7)	18.6 (1.4) (18.0 to 19.2)
2	9.1 (6.1) (7.0 to 11.2)	17.2 (3.7) (15.8 to 18.6)	19.3 (0.9) (18.9 to 19.7)
3	10.1 (6.8) (7.8 to 12.4)	18.0 (3.4) (16.7 to 19.3)	19.0 (1.5) (18.4 to 19.6)
4	13.3 (6.3) (11.1 to 15.5)	19.0 (3.5) (17.7 to 20.3)	19.5 (1.3) (19.0 to 20.0)
5	13.8 (5.9) (11.8 to 15.8)	19.8 (0.8) (19.5 to 20.1)	19.5 (1.2) (19.0 to 20.0)
6	10.1 (6.5) (7.9 to 12.3)	17.8 (3.3) (16.6 to 19.0)	19.8 (0.6) (19.6 to 20.0)
7	7.2 (6.6) (4.9 to 9.5)	15.8 (4.6) (14.1 to 17.5)	19.3 (1.6) (18.6 to 20.0)
8	10.7 (6.7) (8.4 to 13.0)	17.1 (4.1) (15.6 to 18.6)	18.5 (3.1) (17.2 to 19.8)
9	11.4 (7.5) (8.8 to 14.0)	18.9 (2.8) (17.8 to 20.0)	19.4 (1.7) (18.7 to 20.1)
10	12.6 (6.7) (10.3 to 14.9)	19.5 (1.2) (19.0 to 20.0)	19.2 (2.5) (18.2 to 20.2)
11	9.7 (7.1) (7.3 to 12.1)	18.1 (4.1) (16.6 to 19.6)	19.3 (1.7) (18.6 to 20.0)
12	6.2 (6.3) (4.0 to 8.4)	15.7 (6.0) (13.4 to 18.0)	19.3 (1.2) (18.8 to 19.8)

OHT, ocular hypertension.
*See fig 2.

Table 3 Peripapillary thickness (mean (SD) (95% CI) for each of the 12 sectors at 1° from the optic nerve head as quantified by optical coherence tomography

Retinal sector*	Glaucoma	OHT	Control
1	74.9 (32.3) (63.5 to 86.3)	114.7 (24.8) (105.4 to 124.0)	123.4 (22.3) (114.2 to 132.6)
2	70.1 (26.2) (60.8 to 79.4)	101.2 (22.2) (92.8 to 109.6)	119.0 (22.2) (109.8 to 128.2)
3	48.8 (21.2) (41.3 to 56.3)	71.1 (19.4) (63.8 to 78.4)	89.7 (24.3) (79.6 to 99.8)
4	36.6 (12.4) (32.2 to 41.0)	44.9 (14.9) (39.3 to 50.5)	58.0 (15.6) (51.5 to 64.5)
5	46.9 (16.0) (41.2 to 52.6)	60.9 (18.6) (53.9 to 67.9)	68.1 (15.8) (61.6 to 74.6)
6	65.3 (28.7) (55.2 to 75.4)	108.7 (33.6) (96.0 to 121.4)	120.7 (21.5) (111.8 to 129.6)
7	72.4 (33.4) (60.6 to 84.2)	116.1 (28.1) (105.5 to 126.7)	142.1 (17.1) (135.0 to 149.2)
8	54.6 (28.3) (46.6 to 66.6)	101.2 (31.8) (89.2 to 113.2)	121.2 (25.1) (110.8 to 131.6)
9	41.2 (19.0) (34.5 to 47.9)	56.7 (12.5) (52.0 to 61.4)	70.5 (17.3) (63.3 to 77.7)
10	38.0 (19.7) (31.0 to 45.0)	44.7 (8.2) (41.6 to 47.8)	53.8 (10.0) (49.7 to 57.9)
11	51.0 (23.4) (42.7 to 59.3)	73.8 (17.9) (67.1 to 80.5)	88.0 (18.5) (80.3 to 95.7)
12	68.2 (31.1) (57.2 to 79.2)	113.2 (26.9) (103.1 to 123.3)	125.8 (26.7) (114.7 to 136.9)

OHT, ocular hypertension.
*See fig 2.

Table 4 Fundus perimetry (differential light threshold) and optical coherence tomography ability to discriminate glaucomatous from normal eyes

	Fundus-related perimetry (differential light threshold, dB)				OCT (thickness, µm)			
Retinal sector	Cut-off	Sensitivity	Specificity	AROC	Cut-off	Sensitivity	Specificity	AROC
1	14	85.7	100.0	0.98	105	78.8	83.3	0.88
2	17	91.4	100.0	0.97	100	87.9	79.2	0.92
3	16	71.4	100.0	0.93	70	87.9	83.3	0.91
4	19	80.0	87.5	0.88	45	75.8	87.5	0.89
5	19	77.1	87.5	0.85	65	87.9	62.5	0.82
6	18	85.7	100.0	0.95	95	84.8	87.5	0.94
7	18	91.4	91.7	0.96	125	97.0	87.5	0.98
8	20	91.4	75.0	0.88	90	87.9	91.7	0.95
9	18	71.4	91.7	0.85	50	72.7	95.8	0.87
10	20	85.7	79.2	0.87	45	66.7	87.5	0.81
11	17	82.9	95.8	0.91	70	81.8	87.5	0.88
12	17	94.3	95.8	0.97	95	78.8	87.5	0.91
Average	17	94.3	95.8	0.98	80	90.9	100.0	0.99

AROC, area under the receiver operating characteristic curve; OCT, optical coherence tomography.
For each retinal sector, sensitivity and specificity are reported, including the cut-off point at which they are achieved, as well as AROC.

peripapillary DLT. Analysing the AROC of fundus perimetry and OCT of the superior and inferior arcuate fibres, this study shows that in OHT, function of eyes is more altered than morphology, even if the morphological change seems more diffuse (more sectors affected). Average AROC values in table 4 are slightly better for OCT versus fundus perimetry. But AROC data of superior and inferior sectors (1, 7 and 12)

are in favour of fundus perimetry versus OCT. The limited number of altered sectors found with peripapillary fundus perimetry may be related to the DLT of functional damage of specific retinal fibres in these areas. Our data also document that in glaucomatous eyes, fundus perimetry data are more sensitive than OCT in identifying changes in the RNFL of sensitivity:specificity ratio. Moreover, in glaucomatous eyes,

Table 5 Ability of fundus perimetry (differential light threshold) and optical coherence tomography to discriminate ocular hypertension eyes from normal eyes

Retinal sector	Fundus perimetry (differential light threshold, dB)				OCT (thickness, µm)			
	Cut-off	Sensitivity	Specificity	AROC	Cut-off	Sensitivity	Specificity	AROC
1	16	65.5	100.0	0.81	120	58.6	58.3	0.59
2	17	37.9	100.0	0.64	105	58.6	79.2	0.73
3	20	58.6	66.7	0.60	80	75.9	62.5	0.74
4	17	10.3	95.8	0.51	45	51.7	87.5	0.74
5	18	6.9	91.7	0.43	70	69.0	54.2	0.61
6	18	34.5	100.0	0.67	105	55.2	79.2	0.61
7	19	65.5	83.3	0.76	125	65.5	87.5	0.77
8	20	51.7	75.0	0.63	95	48.3	91.7	0.69
9	20	31.0	83.3	0.56	70	89.7	50.0	0.77
10	18	10.3	95.8	0.49	55	86.2	45.8	0.75
11	20	41.4	75.0	0.59	80	69.0	62.5	0.70
12	19	58.6	79.2	0.73	120	62.1	66.7	0.64
Average	19	79.3	79.2	0.78	90	72.4	79.2	0.82

AROC, area under the receiver operating characteristic curve; OCT, optical coherence tomography.
For each retinal sector, sensitivity and specificity are reported, including the cut-off point at which they are achieved, as well as AROC.

AROC values of fundus perimetry in the superior and inferior peripapillary retinal areas are higher than those of OCT. These are the retinal areas where the largest reductions in peripapillary RNFL thickness are reported in OHT and glaucomatous eyes.[19] [29] [30] [34]

In conclusion, whereas OCT measurement of RNFL thickness is currently used for the detection of early RNFL morphological damage in OHT and glaucomatous eyes, topographically related functional information from the same areas may be useful, particularly in eyes without standard visual field loss. Fundus perimetry, therefore, may represent a complement to OCT (and standard automated perimetry) for the detection of early stages of glaucoma.

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