

EXTENDED REPORT

Structural and functional assessment of the macular region in patients with glaucoma

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Purpose: To investigate the correlation of a structural measure of the macular area (optical coherence tomography (OCT)) with two functional measures (10-2 Humphrey visual field (HVF) and multifocal visual evoked potential (mfVEP)) of macular function.

Methods: 55 eyes with open-angle glaucoma were enrolled. The 10-2 HVF was defined as abnormal if clusters of ≥ 3 points with $p < 5\%$, one of which had $p < 1\%$, were present. The mfVEP was abnormal if probability plots had ≥ 2 adjacent points with $p < 1\%$, or ≥ 3 adjacent points with $p < 5\%$ and at least one of these points with $p < 1\%$. Two criteria were used for the macular OCT: (I) ≥ 2 sectors with $p < 5\%$ or 1 sector with $p < 1\%$ and (II) 1 sector with $p < 5\%$.

Results: 54 of the 55 eyes showed an abnormal 10-2 HVF and 50 had central mfVEP defects. The two OCT criteria resulted in sensitivities of 85% and 91%. When both functional tests showed a defect (in 49 eyes), the OCT was abnormal in 45. For the OCT the outer and inner inferior regions were the most likely to be abnormal, and both functional techniques were most abnormal in the superior hemifield.

Conclusions: Good agreement exists between macular thickness and functional defects in patients with glaucoma. Study of the macular region may provide a quantitative measure for disease staging and monitoring.

Despite recent technological advances, the diagnosis of glaucoma is still based on visual field loss and the appearance of the optic disc. Some have suggested that in seeking early diagnosis of glaucomatous damage, it might be advantageous to assess the tissue loss in the peripapillary or macular region.^{1,2} Support for this comes from primate models of glaucoma, where considerable loss of retinal ganglion cells (RGC) occurs in the peripapillary region.^{3,4}

The macular region is rich in RGC bodies and undergoes thinning in glaucoma.^{2,5} Whereas RGCs cannot yet be counted directly in vivo in humans, retinal thickness can be measured with many different techniques. Loss of retinal thickness can be used as a surrogate measure for the loss of RGC bodies and nerve fibre loss, as these layers contribute up to 40% of the entire retinal thickness in normal eyes.^{2,5}

According to Leung *et al.*,⁶ macular retinal thickness, as measured by optical coherence tomography (OCT), can detect glaucomatous damage and corresponds with peripapillary nerve fibre layer (NFL) thickness, a measure of RGC axons as well as glial cells. Thus, the question arises as to how this structural measure (macular thickness) of glaucomatous damage compares with functional measures of macular function. Here we compare OCT measures with two functional measures: the visual fields obtained with standard automated perimetry and the topographical information provided by the multifocal visual evoked potential (mfVEP). With the mfVEP technique, many (typically 60) responses, each associated with a local region of the visual field (or retina), are recorded simultaneously.^{7,8} Compared with other electrophysiological tests of visual function, the mfVEP has the advantage of producing a topographical measure of glaucomatous damage.⁸⁻¹² Thus, mfVEP results can be compared with visual fields obtained with standard automated perimetry,¹³ as well as with structural measures.¹⁴

We investigated the extent to which the structural measure of the macular area (OCT) correlates with two functional measures (10-2 HVF and mfVEP) of macular function.

METHODS

Subjects

The study protocol was approved by the Institutional Review Board for Human Research of the New York Eye and Ear Infirmary, and informed consent was obtained from all subjects before their participation. Procedures adhered to the tenets of the Declaration of Helsinki.

A total of 42 patients (55 eyes) with glaucoma, ranging in age from 25 to 80 years (mean (SD) 62.6 (15.5) years), were prospectively enrolled from the Glaucoma Associates of New York (New York, New York, USA). The types of glaucoma were primary open-angle ($n = 20$), normal-tension ($n = 14$), pseudoexfoliation ($n = 2$), pigmentary ($n = 3$) and chronic closed-angle ($n = 3$).

The inclusion criteria for an eye included visual acuity $\geq 20/40$, no clinical signs of macular disease, refractive error between ± 6.00 diopters (D) spherical and ± 3.00 D cylindrical, glaucomatous optic neuropathy and an abnormal 24-2 HVF. An HVF was considered abnormal if an eye had an abnormal cluster in either hemifield that included the central field defined as ≥ 3 contiguous points in the pattern deviation plot with a p value of $< 5\%$, with one at $< 1\%$. In addition, at least one of 16 central points had to be included in the cluster (four points adjacent to the fixation—fig 1). The mean (SD) deviation of the 24-2 HVF was 9.4 (8) dB. Patients returned for 10-2 HVF, mfVEP and OCT tests.

Visual field testing

Achromatic automated perimetry was performed with a Humphrey Field Analyzer II (model 750, Carl Zeiss Meditec, Dublin, California, USA) using the 24-2 and 10-2 programme with either the full-threshold or the SITA-standard protocol. All patients had 24-2 HVF tests as part of their standard ophthalmological examination. They returned for a 10-2 HVF test.

Abbreviations: HVF, Humphrey visual field; mfVEP, multifocal visual evoked potential; NFL, nerve fibre layer; OCT, optical coherence tomography; RGC, retinal ganglion cells; RNFL, retinal nerve fibre layer

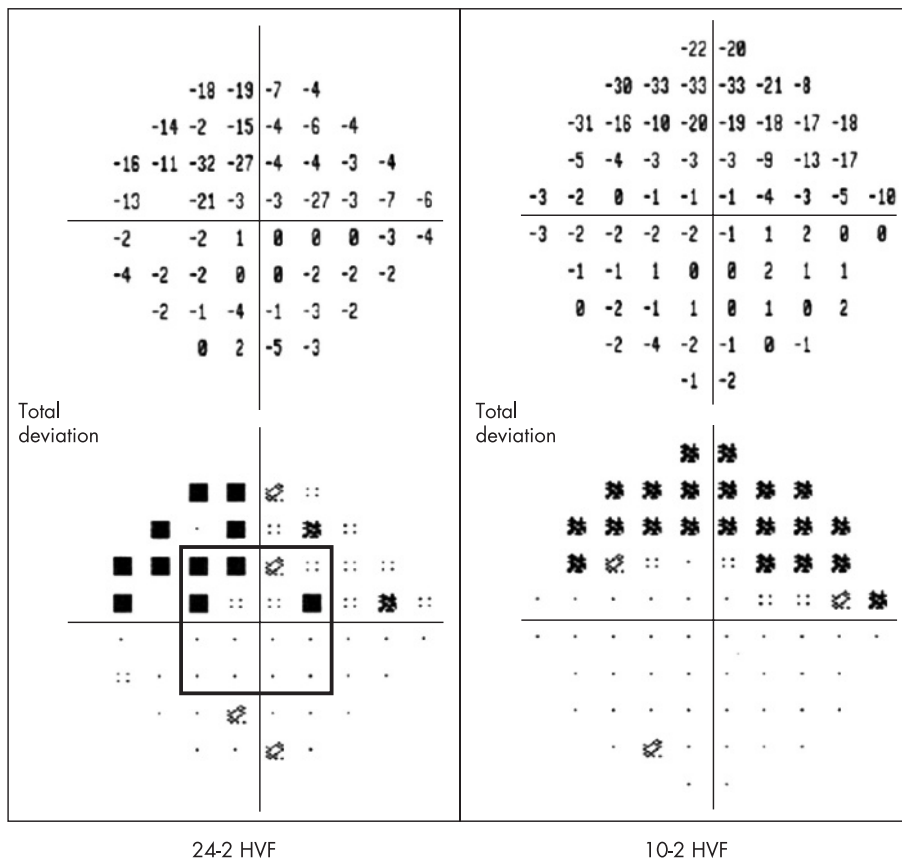


Figure 1 Humphrey visual field 24-2 (left) and 10-2 (right) patterns. Note the central 16 points (square) used for inclusion criteria.

Multifocal visual evoked potentials (mfVEP)

The mfVEP testing was performed on both eyes by a pattern reversal dartboard stimulus (fig 2) and the VERIS software from EDI (Electro-Diagnostic Imaging, San Mateo, California, USA). The dartboard pattern consisted of 60 sectors, each with a checkerboard pattern of 16 checks: 8 white (200 cd/m²) and 8 black (<1 cd/m²). The sectors were scaled with eccentricity to stimulate roughly equal areas of the visual cortex.⁷ The entire display subtended a diameter of 44.5°, and the central 36 sectors fell within 9.8° of the foveal centre (fig 2).

The details of the mfVEP recording and analysis have been published previously.⁸ Briefly, three channels of recording were obtained simultaneously with gold cup electrodes. The ground and reference electrodes were placed on the forehead andinion. One of the three active electrodes was placed 4 cm above the inion, and the other two were placed 1cm above and 4cm on either side of the inion. All three channels were filtered with a high-frequency and a low-frequency cut-off of 3 Hz and 100 Hz, respectively (Grass Instruments preamplifier P511J, Quincy, Massachusetts, USA). An impedance of <5 K was achieved for all subjects. The mfVEPs were low-pass filtered using a sharp cut-off at 35 Hz and a fast Fourier transform technique. This and all other analyses were performed with programs written in MATLAB (Math-Works, Natick, Massachusetts, USA). The exported mfVEP records were processed and an array of best channel responses derived as described previously.^{8 15-17} The amplitudes of each of the 60 local responses were compared with a normative group,¹⁸ and interocular (comparison of two eyes) and monocular probability plots, analogous to the HVF probability plots, were derived.^{8 15}

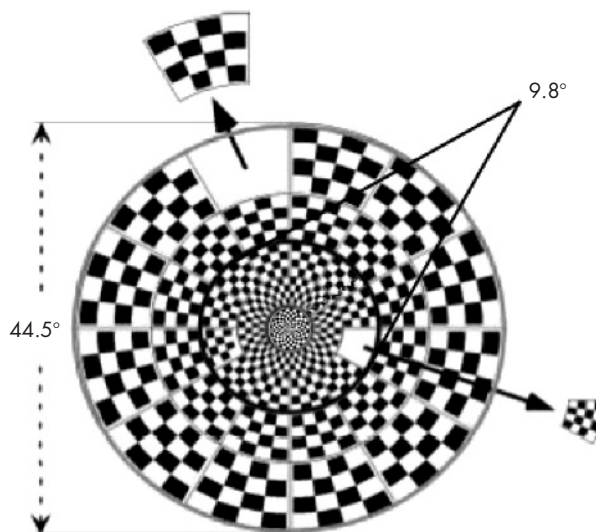


Figure 2 The pattern reversal dartboard stimulus organised in three rings; 36 sectors are within the central 9.8°.

Macular thickness measurements

Macular thickness measurements were made with the Stratus OCT-3 software V 4.0 (Carl Zeiss Meditec, Dublin, California, USA) and the fast macular thickness protocol. The macular scans consisted of six radial scans in a spoke-like pattern centred on the fovea, with each radial scan spaced 30° from one another. The Stratus OCT software calculates retinal thickness as the distance between the vitreoretinal interface

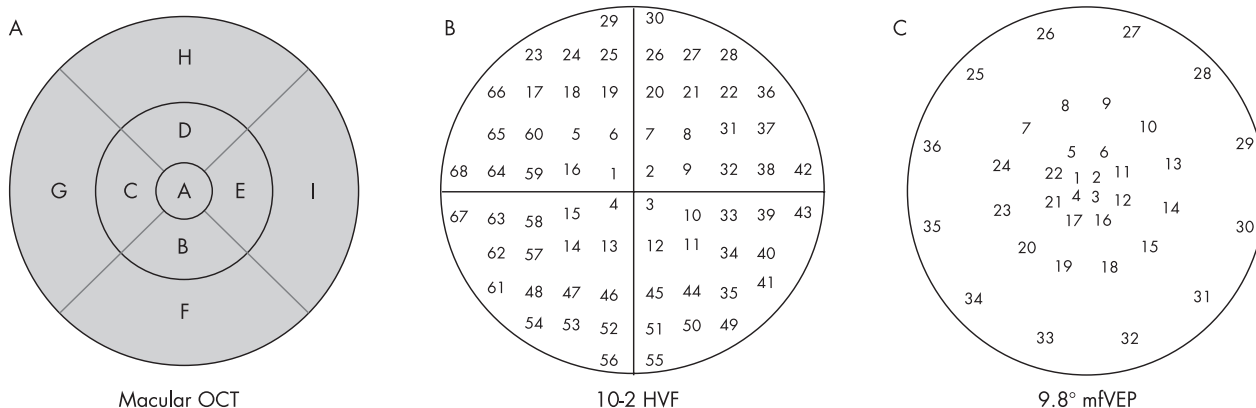


Figure 3 (A) Macular optical coherence tomography (OCT) plot with the nine areas, (B) 10-2 Humphrey visual field (HVF) plot numbered from 1 to 68 and (C) central 9.8° of the multifocal visual evoked potential (mfVEP) plot numbered from 1 to 36.

and the junction between the inner and outer segments of the photoreceptors. Three concentric circles divide the macular thickness map into three zones: fovea, inner macula and outer macula (fig 3A). The inner (B–E) and outer (F–I) zones are further divided into four quadrants by two diagonal lines. Thus, a total of nine regions (fovea, superior outer, inferior outer, inferior inner, temporal outer, temporal inner, nasal outer and nasal inner) are available for analysis.¹⁹

The quality of the scans was evaluated. Scans had to have focused images of the ocular fundus, a signal-to-noise ratio >33 dB, and had to be centred on the fovea. If one scan was classified as unacceptable, the patient was excluded from the study. The minimum pupil diameter was 3 mm.

Criteria for abnormal HVF, mfVEP and OCT tests
Cluster criteria

For the 10-2 HVF, an eye was considered abnormal if there was an abnormal cluster in either hemifield. An abnormal cluster was defined as ≥3 contiguous points in the pattern deviation plot with a p value of <5%, with at least one with a p value of <1%.

The mfVEP was considered abnormal if the interocular or monocular probability plots had an abnormal cluster defined as ≥2 contiguous points with p values <1%, or ≥3 contiguous points with p<5% and with at least one of these points with a p value <1%.

Two criteria were used for the macular OCT: (I) ≥2 sectors with p<5% or 1 sector with p<1% and (II) 1 sector with p<5%.

Point or region criteria

In addition, each HVF or mfVEP point and each OCT region was classified as normal or abnormal according to whether the p value was ≤5%.

Regional comparisons of the techniques

To make regional comparisons of these techniques, we had to take into consideration the fact that the spatial patterns of the three tests differed. Figure 3 shows the test regions of the macular OCT, 10-2 HVF and mfVEP. In all three panels the outer circle has a radius of 10°. The nine regions of the OCT were labelled A–I (fig 3A) and the regions of the 10-2 HVF and mfVEP 1–68 (fig 3B) and 1–36 (fig 3C), respectively. Note that the outer two rings of the mfVEP (fig 2) were omitted from fig 3A as they fell outside 10°. Figure 4 shows how we grouped the 10-2 HVF (left panel) and mfVEP (right panel) test locations into regions compatible with those of the OCT.

RESULTS

On the basis of the cluster criteria, 54 of the 55 eyes (98%) showed an abnormal 10-2 HVF, and 50 (91%) were abnormal on the mfVEP (central 10°). Two criteria were used for the macular OCT: (I) ≥2 sectors with p<5% or 1 sector with p<1% and (II) 1 sector with p<5%. In all, 47 (85%) eyes had abnormal OCTs with Criterion I, and 50 (91%) eyes had abnormal OCTs with Criterion II. Overall, 45 (82%) of the 55 eyes analysed were abnormal on all three tests.

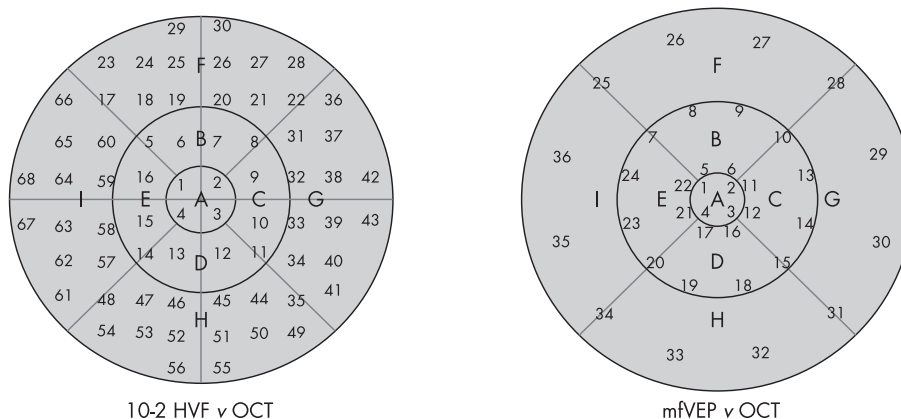


Figure 4 10-2 Humphrey visual field (HVF; left) and multifocal visual evoked potential (mfVEP; right) overlapping the optical coherence tomography (OCT) plot.

Table 1 Number of abnormal and normal eyes

	10-2 HVF				10-2 HVF				mfVEP		
	A	N			A	N			A	N	
mfVEP	A	49	1	OCT (II)	A	49	1	OCT (II)	A	46	4
	N	5	0		N	5	0		N	4	1
Agreement = 89%				Agreement = 89%				Agreement = 85%			

A, abnormal; HVF, Humphrey visual field; mfVEP, multifocal visual evoked potential; N, normal; OCT, optical coherence tomography.

Table 2 Number of abnormal and normal eyes

		10-2 HVF + mfVEP	
		A	N
OCT (I)	A	43	0
	N	6	0
Agreement = 88%			
		A	N
OCT (II)	A	45	0
	N	4	0
Agreement = 92%			

A, abnormal; HVF, Humphrey visual field; mfVEP, multifocal visual evoked potential; N, normal; OCT, optical coherence tomography.

Table 1 shows the pairwise agreement among the three tests. Overall, the agreement between the functional and structural tests (85–89%) was nearly as good as that (89%) between the two functional tests.

Table 2 indicates that when both functional tests (10-2 HVF and mfVEP) were abnormal (49 eyes (89%)), the OCT was abnormal in 43 (88%) (Criterion I) and 45 (92%) (Criterion II) eyes—that is, in four (I) to six (II) eyes the OCT was normal even though both the functional tests were abnormal.

For the macular OCT results, the regions F and B (68% and 49% of the eyes, respectively) were the most likely to be abnormal. The other regions ranged from 2% to 29%. To see if the abnormalities were more likely to appear in a particular part of the field on the 10-2 HVF and mfVEP, we analysed these results after dividing the visual field into regions corresponding to the OCT (fig 4). In the case of the 10-2 HVF, region F (fig 4, left panel), corresponding to the inferior outer macular thickness, was the most affected, with 78% of the points from all 55 eyes showing abnormality at the 5% level, and region B, corresponding to the inferior inner macular thickness, was the second most affected area (superior visual field). For the mfVEP, the same two areas were most affected, with the areas F and B showing 51% and 52% of the points as abnormal, respectively (table 3). Thus, on all three tests, the F and B regions showed the most abnormalities.

DISCUSSION

We investigated the correlation between one structural (OCT) and two functional (10-2 HVF and mfVEP) tests of the macula. To accomplish this, we selected eyes that we assumed had abnormal macular function, on the basis of the results of the 24-2 HVF.

The 10-2 HVF was abnormal in nearly all (98%) eyes. This was not surprising, as we included eyes that had at least one abnormal point out of the 16 central points on the 24-2 HVF. The OCT and mfVEP were abnormal in 91% of the cases. Further, no eye was normal on both functional tests.

There was good agreement between the structural and functional measures. In fact, the macular OCT agreement with the 10-2 HVF and mfVEP (85–89%) was as good as the agreement between the two functional tests. Of the four eyes in which the OCT did not agree with the functional tests, two (50%) had normal-tension glaucoma; in total, 17 (30%) eyes had this type of glaucoma. Perhaps the macular thickness is influenced by intraocular pressure.

There was local agreement as well. The sectors showing more abnormalities on OCT showed more abnormal points on the functional tests. On OCT, the macular region F (outer inferior) was the most affected area, followed by region B (inner inferior). Consistent with these structural findings, both functional techniques showed greater defects in the superior hemifield. Thinning inferiorly has been reported to be the measure most strongly associated with glaucoma status in the NFL and optic nerve head.^{20–22}

Structural damage to the optic nerve head and retinal nerve fibre layer (RNFL) can occur well before any detectable functional visual loss.^{23–25} In addition, the peripapillary RNFL sensitivity^{26–28} is reported to be higher than the macular thickness^{19–20–29} for discriminating between early to moderate glaucomatous and normal eyes. However, all studies comparing sensitivity and specificity between the optic nerve head and the macular region in patients with glaucoma used the 24-2 HVF as the functional criterion. It seems better to compare the macular OCT with the 10-2 HVF, as they are testing the same area. Further, macular thickness scanning is technically easier than NFL thickness scanning, the normal variability of cell density in the central retina being less than that in more peripheral areas^{5–20} and the reproducibility of macular thickness OCT measurements greater than that of

Table 3 Percentage of abnormal points within regions corresponding to the optical coherence tomography sectors

	Abnormal points within each OCT sector (%)								
	A	B	C	D	E	F	G	H	I
10-2 HVF	38	65	39	35	49	78	51	43	58
mfVEP	26	52	31	29	37	51	35	30	45

HVF, Humphrey visual field; mfVEP, multifocal visual evoked potential; OCT, optical coherence tomography.

NFL measurements.³⁰ One important limitation of the macular OCT scan for glaucoma analysis is the choice of sectors. Sectors G, C, A, E and I include portions of the upper and lower hemifields (fig 3). Glaucomatous damage, on the other hand, often respects the midline (fig 1). Although in this study the agreement between the macular OCT and functional tests was very good, in general we would expect the best agreement if the OCT analysis respected the midline. However, currently this information is not readily available to the user.

Although previous studies showed that measurements of macular thickness are no better than measurements of peripapillary NFL thickness for early diagnosis of glaucoma,^{26–28} it is possible that macular testing might be better for monitoring progression. In any case, the OCT scans take relatively little time and there is no reason why both RNFL and macular scans cannot be performed as they provide different information. The health of the macula is more likely to correlate with the patient's quality of life, whereas the RNFL scans provide more global information. Further, the mechanisms and patterns of damage may well differ at these two sites.

In conclusion, our study shows good agreement between macular thickness and functional defects in patients with more advanced disease. The study of the macular region may provide a quantitative measure for disease staging and monitoring.

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