Asymmetry in Hemifield Macular Thickness as an Early Indicator of Glaucomatous Change

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PURPOSE. To investigate whether asymmetry in hemifield macular thickness can serve as an early indicator of glaucomatous structural damage using spectral domain optical coherence tomography.

METHODS. Five zones in the macular thickness map were defined. Each zone included reciprocal areas in the superior and inferior hemifield. Differences in average retinal thickness (DRT) between corresponding regional pairs were measured in each of the five zones in 50 healthy eyes. An abnormality was defined as the DRT value lying outside the 95% confidence intervals. An eye was considered to yield an "abnormal macular hemifield test" (MHT) if abnormality was evident in any zone. The sensitivity and specificity for glaucoma detection of MHT and average circumpapillary retinal nerve fiber layer (cRNFL) classification were determined.

RESULTS. A total of 114 healthy, 103 glaucoma-suspect, and 74 glaucomatous eyes were included. Overall, 5.8%, 36.9%, 88.4%, and 77.4% of the eyes of the healthy, glaucoma-suspect (GS), early glaucoma (EG), and advanced glaucoma (AG) groups yielded abnormal MHT results, respectively. In EG eyes, the sensitivity of an abnormal MHT result was significantly greater than that of abnormal average cRNFL classification ($P = 0.008$). In the GS and AG groups, the sensitivity did not significantly differ between an abnormal MHT result and an average cRNFL classification ($P = 0.880, 0.180$). Compared with sectoral cRNFL thickness measurements, MHT showed a similar level of diagnostic performance. Specificity was not different between an abnormal MHT result and an average cRNFL classification ($P = 0.687$).

CONCLUSIONS. Evaluation of asymmetry in hemifield macular thickness may serve as an assessment tool in the early diagnosis of glaucoma. (*Invest Ophthalmol Vis Sci.* 2012;53:1139–1144) DOI:10.1167/iov.11-8373

Optical coherence tomography (OCT) is currently recognized as an important diagnostic tool in the structural diagnosis of glaucoma. The clinical utility of OCT has been demonstrated in numerous studies.^{1–9}

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Circumpapillary retinal nerve fiber layer (cRNFL) thickness, measured using OCT, is the primary structural assessment strategy used in glaucoma diagnosis. However, because glaucomatous damage involves progressive loss of retinal ganglion cells (RGCs), observation of macular changes has additionally been considered for structural assessment of glaucoma.^{9–18} The macula is the retinal area concerned with central vision and contains approximately 50% of all RGCs. Therefore, macular thickness measurement can be a good target for assessment of glaucomatous structural damage.

The glaucoma hemifield test (GHT), which measures disparity in retinal sensitivity between superior and inferior hemifields, is regarded as very useful in assessment of early glaucomatous changes because damage usually commences in only one horizontal hemifield.^{19–23} Since horizontal hemifield asymmetry is an early indicator of glaucomatous functional damage, it follows that asymmetry in corresponding hemifield retinal thickness should also be indicative of glaucoma. This is because glaucoma is defined as an optic neuropathy characterized by visual field (VF) loss. Therefore, we analyzed asymmetry in hemifield retinal thickness using spectral domain (SD) OCT (Heidelberg Engineering, Dossenheim, Germany). This device yields posterior pole retinal thicknesses from 64 sectors (Fig. 1A). We defined reciprocal pairs of zones on the posterior pole retinal thickness map, in a strategy similar to that by which locations are identified when the GHT is to be conducted. Although orientations of the VF and the macular scan were slightly different, we categorized five regions respecting direction of an RNFL arcade like the way GHT regions in VF were chosen (Fig. 1B). To be more sensitive, we categorized those five regions separating the areas closer to the optic disc and farther from the optic disc like GHT regions in VF were chosen.

We next evaluated asymmetry in horizontal hemifield retinal thickness and analyzed the diagnostic utility for glaucoma detection.

METHODS

Subjects

All study subjects were recruited in a consecutive manner from February 2011 to April 2011 at the glaucoma clinic of the Asan Medical Center, Seoul, Korea. At initial evaluation, all subjects underwent a complete ophthalmologic examination, which included recording medical, ocular, and family history; visual acuity (VA) testing; a commercial field analyzer program (Humphrey field analyzer [HFA] Swedish Interactive Threshold Algorithm 24 to 2 test; Carl Zeiss Meditec, Dublin, CA); multiple intraocular pressure (IOP) measurements using Goldmann applanation tonometry; stereoscopic optic nerve photography; and SD-OCT imaging. All patients with glaucoma had extensive experience with HFA testing. To minimize the learning effect, data from the second HFA tests were used in analysis. For inclusion in the study, all participants had to meet the following criteria: best-corrected

FIGURE 1. Posterior pole retinal thickness map showing the 64 sectors used in spectral domain optical coherence tomography (A) and the five zones used for assessment of asymmetry in hemifield macular thickness (B).

VA of 20/30 or better, with a spherical refractive error within ± 5 diopters (D) and a cylinder correction within $+3$ D; the presence of a normal anterior chamber and open-angle on slit-lamp and gonioscopic examinations; and reliable HFA test results with a false-positive error $< 15\%$, a false-negative error $< 15\%$, and a fixation loss $< 20\%$. Subjects with any other ophthalmic disease that could result in HFA defects, or with a history of diabetes mellitus or intraocular surgery, were excluded. One eye was randomly selected if both eyes were found to be eligible. Age-matched healthy eyes formed the control group. Control eyes were those of clinic staff, family members thereof, spouses of patients, or volunteers from our eye clinic and hospital. No member of the control group had any history of ocular symptoms or disease and had not undergone intraocular incisional or laser surgery. All control eyes had IOP values < 22 mm Hg, with no history of IOP elevation, and were normal by VF examination. Glaucomatous eyes were defined as those in which glaucomatous VF defects were confirmed on at least two VF examinations yielding reliable data, and by the presence of a glaucomatous optic disc that showed an increase in cupping (vertical cup-disc ratio > 0.6), a difference in the vertical cup-disc ratio of > 0.2 between eyes, diffuse or focal neural rim thinning, or hemorrhage, as agreed on by two glaucoma experts (JHN, KRS). Eyes with glaucomatous VF defects were defined as those with a GHT result outside normal limits or a pattern SD (PSD) outside 95% of normal limits. Additionally, a cluster of three points with probabilities of $< 5\%$ on the pattern deviation map in at least one hemifield, including at least one point with a probability of $< 1\%$; or a cluster of two points with a probability of $< 1\%$ was needed. Glaucoma-suspect eyes included those with a glaucomatous disc but with a normal VF.

All procedures conformed to the Declaration of Helsinki and the participants signed an informed consent; the study was approved by the Institutional Review Board of the Asan Medical Center at the University of Ulsan, Seoul, Korea.

SD-OCT Imaging

Macular thickness was measured using the SD-OCT (Spectralis OCT, Heidelberg Engineering) posterior pole analysis mode. cRNFL thickness was determined using the same device during the same session. Macular thickness was calculated as the distance between the vitreoretinal interface and the outer border of retinal pigment epithelium. Imaging was performed on each subject at the time when VF was assessed, or within 2 weeks thereof. Only images of good quality were accepted. Such images were correctly focused, evenly illuminated as revealed by reflectance, and centered on the optic disc or macula. The images with eye motion in the en face image presented as discontinuity of blood vessels were excluded.

Analysis

Of the healthy eyes, a randomly chosen group of 50 eyes (reference group) was used to determine cutoff values for differences in average

retinal thickness between reciprocal regions in each of the five chosen zones. Data from the remaining 64 healthy eyes (the test group) were used to determine the sensitivity and specificity of asymmetry measurements in hemifield macular thickness for glaucoma detection. A macular thickness map yielded by posterior pole analysis is divided into 64 sectors centered on the fovea (Fig. 1A). In the present study, we arbitrarily divided both the superior and inferior hemifields into five zones; each zone included reciprocal regions from either hemifield (Fig. 1B). Average retinal thickness of each of the five zones was measured in both the superior and inferior hemifields. Differences in retinal thickness values (DRTs) between corresponding pairs of locations were calculated. For example, the DRT 1 value was the difference between superior zone 1 and inferior zone 1. Means, SDs, and 95% confidence intervals (CIs) of DRT values for each of the five regions were determined using data from the reference group. If a test DRT value exceeded the 95% CI for any zone, that zone was considered to be abnormal in healthy (test group), glaucoma-suspect, and glaucomatous eyes. If at least one of the five regions exhibited such an abnormality, that eye was considered to yield an "abnormal macular hemifield test (MHT)" result. Thus, the prevalence of abnormal MHT results was determined in healthy (test group), glaucoma-suspect, and glaucomatous eyes.

To compare the sensitivity and specificity of abnormal MHT results in terms of the capacity to detect glaucoma at different stages, we divided glaucomatous subjects into two groups, an early group (EG) and a moderate-to-advanced group (AG), using the Hodapp-Anderson-Parrish (HAP) scale that grades VF severity. This staging system is described in detail elsewhere.^{24,25}

In terms of cRNFL thickness, SD-OCT (Spectralis) provides an average of four quadrants (superior, inferior, nasal, and temporal) and six sectoral (temporal-superior, temporal-inferior, temporal, nasal-superior, nasal-inferior, and nasal) cRNFL thickness classifications. We used two criteria for defining cRNFL thickness abnormality. If the average cRNFL thickness value was $< 5\%$ of that in the normative inbuilt database, it was considered to be abnormal (cRNFL 1). If any four-quadrant or six-sector cRNFL thickness value was $< 5\%$ of that in the normative inbuilt database, it was considered to be abnormal (cRNFL 2).

The sensitivity and specificity values of abnormal MHT results, in terms of detection of glaucomatous and glaucoma-suspect eyes, were obtained and compared with those afforded by cRNFL 1 and cRNFL 2 thickness measurements, using the McNemar test.

Statistical analysis was performed using commercial software (SPSS version 15.0; SPSS Inc., Chicago, IL).

RESULTS

A total of 114 healthy, 103 glaucoma-suspect, and 74 glaucomatous eyes were included in the present study. Among the

114 healthy eyes, a randomly chosen group of 50 were analyzed to determine DRT cutoff values to be used in the detection of abnormalities (the reference group), whereas data from the remaining 64 eyes (the test group) were used to estimate sensitivity and specificity.

The average VF mean deviation in the glaucoma group was -7.5 ± 7.1 dB. All study participants were Asian (Korean), and mean subject age did not differ significantly among the healthy, glaucoma-suspect (GS), and glaucomatous groups. As expected, the average cRNFL thickness and macular thickness differed significantly among the three groups (Table 1). Forty-three eyes were categorized to the EG group, and 31 eyes the AG group, using the HAP scale that assesses the severity of VF loss.^{24,25}

The DRT cutoff values for zones 1, 2, 3, 4, and 5, as obtained by comparison with reference group data, were 10.4, 8.8, 7.7, 11.2, and 11.7 μm , respectively. These values were used to determine the prevalence of abnormal zones. For example, a DRT test value $> 10.4 \mu\text{m}$ when the zone 1 regions of the superior and inferior hemifields were compared was indicative of abnormality. The percentages of eyes abnormal by DRT assessment in each of the five zones and MHT result are shown in Table 2. Among the five zones, zones 2 and 5 showed the highest prevalence of abnormalities in both EG and AG eyes (51.2% and 51.6% in zone 2, and 55.8% and 58.1% in zone 5, respectively; Table 2). Overall, 5.8%, 36.9%, 88.3%, and 77.4% of healthy, GS, EG, and AG eyes, respectively, were abnormal in at least one of the five regions, and were thus considered to yield an abnormal MHT result.

The sensitivities and specificities for glaucoma detection using the MHT and both cRNFL 1 and cRNFL 2 thickness classification were determined. In the GS group, the sensitivity of an abnormal MHT was 36.9%, which was not significantly different from that afforded by an abnormal cRNFL 1 classification (35.9%, $P = 0.880$). In the EG group, the sensitivity of an abnormal MHT result (88.3%) was significantly higher than that of an abnormal cRNFL 1 classification (66.0%, $P = 0.008$). However, in the AG group, the sensitivity of an abnormal MHT result was not significantly different from that of abnormal cRNFL 1 classifications (77.4%, 93.5%, $P = 0.180$). When we compared the sensitivity of cRNFL 2 classification with that of MHT, all three groups, GS, EG, and AG, did not show a signif-

icant difference ($P = 0.766, 1.00, 0.070$). The specificity of an abnormal MHT result was not different from that of either cRNFL 1 or cRNFL 2 classification (Table 3).

DISCUSSION

Glaucoma is associated with characteristic structural changes in the optic disc and the RNFL, accompanied by functional VF loss. Thus, both structural and functional assessments are mandatory in glaucoma diagnosis. Often, structural change precedes functional deficit, as assessed by standard automated perimetry.^{26–28} Thus, structural evaluation of the optic disc and RNFL has been used to detect early glaucomatous changes. The recent development of imaging technologies allowing quantification of such structural changes may contribute to earlier detection of glaucomatous damage. Among various structural parameters, RNFL examination is an important tool for structural assessment of glaucoma. In the interval since the introduction of OCT, most studies have focused on cRNFL thickness assessment because the RNFL layer is thicker in this region than that in other parts of the retina, which makes measurement efficient. Because improvements in technology gradually made it possible to obtain volumetric data and quantify retinal thickness in the macular area, many studies have sought to determine whether changes in this region might afford an alternative means of detecting glaucoma development.^{9–18} Several studies showed the possibility of macular thickness as an alternative tool to cRNFL as a strategy for structural assessment of glaucomatous damage; however, the diagnostic capability of macular thickness measurements were generally inferior to that of cRNFL examination in terms of glaucoma diagnosis.^{9,10,13,16} Using time domain OCT, Wollstein et al.⁹ reported that optic nerve head and NFL parameters provided similar discrimination capabilities between healthy eyes and those of glaucoma patients and superior discrimination capabilities when compared with macular parameters. Parikh et al.¹⁶ reported that macular parameters had moderate sensitivity and specificity and thus the role of macular parameters in the diagnosis of early glaucoma was limited using the same device. Na et al.¹⁸ recently categorized glaucomatous eyes into two groups, one in which the cRNFL thickness

TABLE 1. Demographics and Visual Field and Spectral Domain Optical Coherence Tomography Data from Healthy, Glaucoma-Suspect, and Glaucomatous Subjects

Parameter	Healthy (<i>n</i> = 64)	Glaucoma-Suspect (<i>n</i> = 103)	Glaucomatous (<i>n</i> = 74)	<i>P</i>
Age, y	50.8 $\pm$ 11.6	52.5 $\pm$ 13.7	52.9 $\pm$ 14.1	0.229
Male/female	30/39	43/60	33/41	0.589
VF MD, decibels	-0.3 ± 1.2	-0.8 ± 1.3	-7.5 ± 7.1	0.98* <0.001** <0.001***
VF PSD, decibels	1.6 $\pm$ 0.7	1.6 $\pm$ 0.4	6.9 $\pm$ 4.0	1.0* <0.001** <0.001***
VF VFI, %	99.0 $\pm$ 1.4	99.0 $\pm$ 0.9	80.0 $\pm$ 22.0	1.0* <0.001** <0.001***
Average cRNFL thickness, μm	102.0 $\pm$ 8.6	85.2 $\pm$ 11.5	70.8 $\pm$ 14.4	<0.001* <0.001** <0.001***
Average macular thickness, μm	296.0 $\pm$ 14.0	281.0 $\pm$ 24.8	270.0 $\pm$ 13.1	0.002* <0.001** <0.001***

Comparisons among the three groups were performed using ANOVA, with the Bonferroni post hoc comparison (*healthy vs. glaucoma-suspect, **glaucoma-suspect vs. glaucomatous, ***healthy vs. glaucomatous). MD, mean deviation; VFI, visual field index.

TABLE 2. Differences in Average Retinal Thickness between the Superior and Inferior Hemifields (Five Zones) and the Percentages of Eyes Abnormal by DRT Assessment

Group	Abnormal MHT* % (n)	Zone 1			Zone 2			Zone 3			Zone 4			Zone 5		
		DRT†	% (n)		DRT†	% (n)		DRT†	% (n)		DRT†	% (n)		DRT†	% (n)	
Healthy (n = 64)	5.8 (4)	8.9 ± 6.3	2.9 (2)		5.9 ± 5.3	1.4 (1)		5.5 ± 4.7	2.9 (2)		7.1 ± 6.8	5.8 (4)		9.5 ± 7.1	2.9 (2)	
Glaucoma-suspect (n = 103)	36.9 (38)	8.9 ± 8.1	9.7 (10)		8.8 ± 8.2	11.7 (12)		6.7 ± 8.5	9.7 (10)		9.3 ± 8.0	13.6 (14)		11.4 ± 10.5	16.5 (17)	
Early glaucoma (n = 43)	88.3 (38)	12.8 ± 13.3	23.3 (10)		17.5 ± 12.9	51.2 (22)		12.1 ± 13.0	30.2 (13)		17.7 ± 12.2	41.9 (18)		23.3 ± 16.1	55.8 (24)	
Advanced glaucoma (n = 31)	77.4 (24)	11.4 ± 9.1	29.0 (9)		19.8 ± 16.0	51.6 (16)		9.7 ± 13.9	22.6 (7)		20.5 ± 16.0	41.9 (13)		30.1 ± 21.4	58.1 (18)	

* An abnormal macular hemifield test (MHT) result was defined as an abnormality in any of the five zones.

† Data are shown as mean ± SD.

TABLE 3. Sensitivity and Specificity (%) of MHT and RNFL Thickness Measurements in Terms of Glaucoma Detection

Group	Sensitivity					Specificity					**P
	RNFL 1	RNFL 2	MHT	*P	**P	RNFL 1	RNFL 2	MHT	*P	**P	
Glaucoma-suspect	35.9 (26.0–46.0)	39.8 (30.4–49.9)	36.9 (27.8–47.0)	0.8 80	0.7 66	96.9 (88.2–99.5)	96.9 (88.2–99.5)	93.8 (84.0–98.0)	0.6 87	0.6 25	
Early glaucoma	66.0 (50.6–78.7)	86.0 (71.4–94.2)	88.3 (74.1–95.6)	0.0 0.8	1.0 0.0	96.9 (88.2–99.5)	96.9 (88.2–99.5)	93.8 (84.0–98.0)	0.6 87	0.6 25	
Advanced glaucoma	93.5 (77.2–98.9)	96.8 (81.5–99.8)	77.4 (58.5–89.7)	0.1 80	0.0 7	96.9 (88.2–99.5)	96.9 (88.2–99.5)	93.8 (84.0–98.0)	0.6 87	0.6 25	

* P value comparisons between MHT and cRNFL 1 classification.

** P value comparisons between MHT and cRNFL 2 classification using McNemar test.

performed better and another in which macular thickness performed better, and found approximately three times as many eyes were placed in the cRNFL group. One explanation was that since macular thickness included areas not specific for glaucoma, diagnostic sensitivity decreased. Recently, it has become possible to selectively measure the thickness of the inner layer of the macula, leading to interest in the use of such measurements in the early detection of glaucoma.^{14,15,17} Tan et al.¹⁴ demonstrated that thinning of the macular NFL, ganglion cell layer, and inner plexiform layer is detectable even before visual field changes are noted. Seong et al.¹⁵ reported that inner retinal thickness showed glaucoma discrimination ability comparable to that of cRNFL thickness in glaucoma patients with early VF defects. Therefore, although such inner macular layer thickness measurement showed a level of diagnostic performance similar to that of cRNFL in detecting early glaucoma, it did not outperform cRNFL thickness measurement. Thus, we used a novel approach that compared superior and inferior hemifield thickness.

The GHT, performed using a commercial field analyzer program (Humphrey STATPAC; Allergan Humphrey, San Leandro, CA), measures and compares the differences in the sums of threshold values in five reciprocal superior and inferior sectors chosen with respect to the normal anatomy of the RNFL.²⁹ Johnson et al.³⁰ have documented the high sensitivity and specificity of a GHT result "outside normal limits" in the detection of early glaucomatous functional damage. An abnormal GHT result is very helpful in the diagnosis of glaucomatous change.^{19–23,30} In particular, an abnormal GHT result is a sensitive indicator of early-stage disease.³⁰ This is because the characteristic symmetric distribution of retinal nerve fibers with reference to the horizontal raphe is perturbed when glaucoma develops. Thus, asymmetric development of a defect in either the superior or inferior hemifield is indicative of glaucomatous change. Because structural change is often accompanied by functional deficit, we hypothesized that the rate of macular thickness loss might differ in the superior and inferior hemispheres, as is apparent when VF assessment is performed using the GHT. To explore this idea, we simulated the GHT approach by choosing particular regions on the macular sectoral map and comparing superior and inferior hemimacular thickness; this test is abbreviated as MHT in the present work. If it is considered that structural change precedes functional loss, asymmetric macular changes may serve as early indicators of such change.

Just as GHT plays the role as a sensitive global index for early detection of glaucomatous VF change, it would be desirable if there are sensitive global indices in OCT measurement for early detection of glaucomatous structural change. Average cRNFL thickness may be a single parameter that represents global status of structural glaucomatous change. We found that the MHT result was similar in terms of sensitivity to average cRNFL thickness measurements in the GS and AG groups. However, the MHT result was significantly higher in terms of sensitivity than average cRNFL thickness measurement in the EG group. In other words, the MHT was at least as sensitive as average cRNFL measurements in eyes with preperimetric glaucoma and more sensitive in early stage of glaucoma. In AG eyes, the sensitivity of the MHT was lower than that of average cRNFL thicknesses, although it did not reach a statistically significant level. This may be because diffuse reduction in both superior and inferior macular thickness is evident at advanced stages of glaucoma. In the mean time, glaucoma usually begins with localized change and thus average cRNFL measurements may be insensitive in detecting early and localized change. Therefore, we included another criterion, RNFL 2 classification, which defined abnormality as if there were abnormality in any quadrant or sector. When we compared the sensitivity of

RNFL 2 classification and that of MHT, all three groups, GS, EG, and AG, did not show a significant difference. In other words, MHT showed a similar level of performance when defining abnormality as the appearance of any sectoral abnormality. In terms of specificity, the MHT showed a level similar to that of cRNFL measurements. Therefore, considering our observation that MHT showed better performance in terms of glaucoma detection in early stage than average cRNFL measurements and a level of diagnostic capacity similar to that of any sectoral cRNFL measurements with a decent level of specificity, we may suggest MHT as possibly one global parameter that can represent the structural status of glaucoma.

We used 50 controls in MHT since this analysis was novel and designed by ourselves and, thus, an inbuilt database was not available. We repeated the analysis using 50 controls with cRNFL and it actually yielded the same result (data not shown). Since the presenting result derived from two kinds of normative database may be complicated and the results were actually same, we did not provide the result of cRNFL by our own 50 controls. We believe the cRNFL inbuilt database is more important, since it is a reference standard for users of this device.

To the best of our knowledge, no prior study has explored differences in retinal thickness between reciprocal zones in the upper and lower hemispheres. Leung et al.³ conducted macular thickness mapping in which they collected data from the circumferences of three concentric circles centered on the fovea, using circle diameters of 1, 3, and 6 mm. When the characteristic arching and symmetric distribution of retinal nerve fibers above and below the fovea of the posterior pole are considered, retinal thickness mapping along horizontal lines may also be useful in sectoral assessment of macular thickness.

Of the five zones, data from zones 2 and 5, located nasally to the macula, afforded the highest sensitivity values. These zones lie close to the optic disc. The possible speculation is that the nasal side of the macula conveys fibers that come from both nasal and temporal sides of the macula, whereas the temporal side contains only the temporal side, which leads to a worse performance than the nasal aspect. Moreover, zones 2 and 5 contain superior and inferior arcuate nerve fibers that are vulnerable to early glaucomatous change.

In conclusion, the MHT showed better performance than average cRNFL thickness measurements in terms of diagnostic sensitivity in eyes with early-stage glaucoma, with a similar level of specificity; moreover, the MHT was similar to average cRNFL thickness measurements in detecting preperimetric or advanced-stage glaucoma. Compared with sectoral cRNFL thickness measurement, MHT showed a similar level of diagnostic performance. Measurement of asymmetry in macular hemifield thickness may be a useful alternative diagnostic aid in the detection of glaucoma, especially early-stage disease. Modification of the MHT algorithms or assessment of only the thickness in the macular inner layer may improve the diagnostic utility of the test.

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