• Clinical Research •

Discriminating performance of macular ganglion cell-inner plexiform layer thicknesses at different stages of glaucoma

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Abstract

• AIM: To determine the discriminating performance of the macular ganglion cell-inner plexiform layer (GC-IPL) parameters between all the consecutive stages of glaucoma (from healthy to moderate-to-severe glaucoma), and to compare it with the discriminating performances of the peripapillary retinal nerve fiber layer (RNFL) parameters and optic nerve head (ONH) parameters.

• METHODS: Totally 147 eyes (40 healthy, 40 glaucoma suspects, 40 early glaucoma, and 27 moderate-to-severe glaucoma) of 133 subjects were included. Optical coherence tomography (OCT) was obtained using Cirrus HD-OCT 5000. The diagnostic performances of GC-IPL, RNFL, and ONH parameters were evaluated by determining the area under the curve (AUC) of the receiver operating characteristics.

• RESULTS: All GC-IPL parameters discriminated glaucoma suspect patients from subjects with healthy eyes and moderate-to-severe glaucoma from early glaucoma patients (*P*<0.017, for all). Also, minimum, inferotemporal and inferonasal GC-IPL parameters discriminated early glaucoma patients from glaucoma suspects, whereas no RNFL or ONH parameter could discriminate between the two. The best parameters to discriminate glaucoma suspects from subjects with healthy eyes were superonasal GC-IPL, superior RNFL and average c/d ratio (AUC=0.746, 0.810 and 0.746, respectively). Discriminating performances of all the parameters for early glaucoma *vs* glaucoma suspect comparison were lower than that of the other consecutive group comparisons, with the best GC-IPL parameters being minimum and inferotemporal (AUC=0.669 and 0.662, respectively). Moreover, minimum GC-IPL, average RNFL, and rim area (AUC=0.900, 0.858, 0.768, respectively) were the best parameters for discriminating moderate-to-severe glaucoma patients from early glaucoma patients.

• CONCLUSION: GC-IPL parameters can discriminate glaucoma suspect patients from subjects with healthy eyes, and also all the consecutive stages of glaucoma from each other (from glaucoma suspect to moderate-to-severe glaucoma). Further, the discriminating performance of GC-IPL thicknesses is comparable to that.

• KEYWORDS: retinal nerve fiber layer; optic nerve head; cirrus HD-OCT; ganglion cell-inner plexiform layer; glaucoma suspect

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INTRODUCTION

Glaucoma is one of the leading causes of blindness owing to the depletion of retinal ganglion cells (RGCs)[1]. The diagnosis of glaucoma is based on observations of structural damage to the optic nerve head (ONH), and/or the retinal nerve fiber layer (RNFL), as well as associated visual field (VF) findings. Previous studies have shown that depletion of RGCs can occur before clinical detection of VF defects[2-4]. In recent years, it has become possible to evaluate structural damage objectively and quantitatively with improvements in imaging technologies, particularly with optical coherence tomography (OCT). Currently, glaucoma diagnosis and follow-up mostly focus on peripapillary RNFL and ONH parameters. However, glaucoma specialists have also begun to consider inner retinal thickness measurements determined by visualization of the inner retinal layers on high-resolution spectral domain OCT (SD-OCT). Evaluation of the macular region of the retina for early detection of glaucoma has become increasingly important because it has been determined that 50% of RGCs

are present in this area[5]. Hence, macular ganglion cell thickness parameters have been established using segmentation algorithms.

Studies with Fourier-domain OCT have shown that ganglion cell complex (GCC) measurements including the ganglion cell layer, inner-plexiform layer, and RNFL were found to be as effective as peripapillary RNFL and ONH measurements for discriminating glaucomatous eyes from healthy eyes[6-7]. However, the GCC is influenced by the inter-individual variations in the human retina as it contains the macular RNFL. Cirrus HD-OCT 5000 (Carl Zeiss Meditec, Dublin, CA, USA) is a SD-OCT device which can measure macular ganglion cell-inner plexiform layer (GC-IPL) thickness using a previously described ganglion cell analysis (GCA) algorithm[8]. GCA segments the macular RNFL layer from the GC-IPL which sets it apart from the GCC measurements. Measurements of the GC-IPL are thought to be less affected by inter-individual variation compared with RNFL thickness measurements[9].

Discriminating performance of ganglion cell layer thickness measurements at different stages of glaucoma were investigated in the previous studies[10-11]. However, different results for the discriminating performances have been reported when compared to those of the RNFL measurements, and the ONH measurements, among the previous studies. Also, the diagnostic performance of GC-IPL parameters for discriminating glaucoma suspects from those with early glaucoma still needs to be investigated, since their management is challenging, and also there is limited data available in the literature. We aimed to determine the discriminating performance of macular GC-IPL parameters between all the consecutive stages of glaucoma (from healthy to moderate-to-severe glaucoma), and to compare it with the discriminating performances of the peripapillary RNFL parameters, and the ONH parameters evaluated in this study.

SUBJECTS AND METHODS

Ethical Approval This prospective, cross-sectional study was approved by the Ethical Committee of Haseki Training and Research Hospital, Istanbul, Turkey and adhered to the tenets of Declarations of Helsinki. Informed consent was obtained from the subjects after explanation of the nature and the possible consequences of the study.

Subjects A total of 147 eyes (40 glaucoma suspect, 40 with early glaucoma, and 27 with moderate-to-severe glaucoma, as well as 40 healthy) of 133 subjects were included in the study between August 2015 and December 2015. If both the eyes of the patients were at the same stage of the disease, only one eye was randomly included in the study.

Inclusion criteria were glaucoma suspect and primary open angle glaucoma (POAG), age between 40 and 80y, best corrected visual acuity (BCVA) ≥20/40, refractive error within ±5.00 D equivalent sphere and ±3.00 D astigmatism, no retinal diseases (diabetic retinopathy, hypertensive retinopathy, macular degeneration, and epiretinal membrane), absence of non-glaucomatous optic nerve diseases, no systemic treatments which had possibly caused toxicity to the retina or optic nerve (chloroquine and amiodarone), and no laser therapy or ocular surgery except for uncomplicated cataract surgery. All subjects in the study underwent a comprehensive ophthalmologic examination, which included evaluation of medical history, non-cycloplegic refraction, BCVA measurement, slit lamp biomicroscopy, intraocular pressure (IOP) measurement by Goldmann applanation tonometry, gonioscopy, dilated fundus examination, corneal pachymetry, VF examination using a Humphrey Field Analyzer II 740 (Carl Zeiss Meditec), and SD-OCT imaging (Cirrus HD-OCT 5000; Carl Zeiss Meditec). The criteria for healthy eyes included normal optic disc appearance, normal VF examination, and IOP≤21 mm Hg. Glaucoma suspect eyes were those having ocular hypertension (OHT; IOP>21 mm Hg) with a normal optic disc and normal VF examination, or those with glaucomatous optic disc appearance and normal VF examination. Glaucomatous eyes were those having glaucomatous VF defects, glaucomatous optic disc damage (c/d ratio ≥0.5, c/d ratio asymmetry ≥0.2, optic disc hemorrhage, focal thinning, and notching of the neuroretinal rim), and IOP≥21 mm Hg. Based on the Hodapp-Parish-Anderson criteria[12], patients were staged into early glaucoma, moderate glaucoma, and severe glaucoma groups. Subsequently, the patients with moderate or severe glaucoma were grouped to form moderate-to-severe glaucoma group to simplify the comparison between glaucoma suspect patients, patients with early glaucoma, and those with more severe glaucomatous damage than that in early glaucoma. All patients with different stages of POAG were stable and controlled with glaucoma medications upon enrollment into the study.

Visual Field Testing VF examination was performed using the Swedish interactive threshold algorithm (Humphrey Field Analyzer II 740, 30-2 SITA Standard; Carl Zeiss Meditec). The reliability criteria for VFs required the fixation losses, and the false-positive and false-negative response rates to be less than or equal to 20%. Only patients who had at least two consecutive reliable VF examinations were enrolled in the study.

Optical Coherence Tomography Measurements SD-OCT imaging was obtained by using the Cirrus HD-OCT 5000 (Carl Zeiss Meditec). OCT was carried out using the macular cube 200×200 protocol for GCA, and the optic disc cube 200×200 protocol for peripapillary RNFL and ONH parameters, as described before[8,13]. The OCT images were acquired through dilated pupils by the same operator, and only images with a signal strength of 6 or greater were included in this study.

Table 1 Demographics and clinical characteristics of subjects mean±SD

Parameters	Healthy eyes (40 eyes)	Glaucoma suspect (40 eyes)	Early glaucoma (40 eyes)	Moderate-to-severe glaucoma (27 eyes)	*P*	P^b	P^c	P^d
Age[a], y	56.1±7.7	56.3±8.9	57.9±8.9	62.4±8.9	0.016	0.925	0.423	0.044
Sex, *n* (%)								
Female	20 (50.0)	26 (65.0)	19 (47.5)	13 (48.1)	0.362			
Male	20 (50.0)	14 (35.0)	21 (52.5)	14 (51.9)				
BCVA	0.99±0.04	0.97±0.07	0.97±0.08	0.86±0.25	<0.001	0.475	0.945	0.001
IOP, mm Hg	15.2±2.4	17.7±3.4	16.9±3.0	17.4±4.4	0.009	0.001	0.259	0.797
Visual field								
MD, dB	-1.58±1.05	-1.92±0.89	-3.66±1.28	-15.05±7.85	<0.001	0.191	0.000	0.000
PSD, dB	1.72±0.43	1.92±0.67	3.42±1.40	8.27±2.78	<0.001	0.107	0.000	0.000
CCT, μm	554.9±30.7	549.3±41.9	545.5±38.5	540.8±39.0	0.466			

BCVA: Best corrected visual acuity; IOP: Intraocular pressure; MD: Mean deviation; PSD: Pattern standard deviation; CCT: Central corneal thickness; SD: Standard deviation. Bonferroni correction $P<0.017$; [a]Parametric test $P<0.05$. P^b values for comparing glaucoma suspect and healthy groups; P^c values for comparing early glaucoma and glaucoma suspect groups; P^d values for comparing moderate-to-severe glaucoma and early glaucoma groups.

The analyzed macular GC-IPL thickness measurements were average, minimum, superior, superonasal, inferonasal, inferior, inferotemporal, and superotemporal thicknesses; the peripapillary RNFL parameters were average, superior, inferior, temporal, and nasal thicknesses; and the ONH parameters were disc area, rim area, vertical c/d ratio, average c/d ratio, and cup volume.

Statistical Analysis Statistical Package for the Social Sciences (SPSS) for Windows version 15.0 (SPSS, Inc., Chicago, IL, USA) was used for the statistical analyses. The descriptive statistics applied were, count and ratio for categorical variables, and the mean and standard deviation for numeric variables. The variables were evaluated using visual (histograms, probability plots) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether they were normally distributed. To compare the numeric variables of more than two independent groups, a one-way ANOVA test for normally distributed variables and a Kruskal-Wallis test for non-normally distributed variables were used. Sub-group analyses were performed with parametric Tukey test and nonparametric Mann-Whitney *U* test and adjusted with Bonferroni correction. The Chi-square test was used to compare the proportions of categorical variables in different groups, Bonferroni correction was applied. Area under the curve (AUC) values of the receiver operating characteristic (ROC) were used to determine the diagnostic performances of GC-IPL, RNFL, and ONH test parameters. A *P*-value less than 0.05 was considered statistically significant.

RESULTS

Demographic and clinical characteristics of the subjects are shown in Table 1. There were no statistically significant age differences between subjects with healthy eyes and the glaucoma suspects (P=0.925), and between glaucoma suspects and early glaucoma patients (P=0.423), whereas statistically significant difference was present between early glaucoma patients and moderate-to-severe glaucoma patients (P=0.044). The BCVA of the participants was similar except for the moderate-to-severe glaucoma patients, who had significantly lower BCVA compared with the early glaucoma patients (P<0.001). The mean deviation (MD), and the pattern standard deviation (PSD) of VFs were significantly different between the consecutive groups, except for the healthy and glaucoma suspect groups (P=0.191, for MD value; P=0.107, for PSD value).

Table 2 shows the GC-IPL, RNFL, and ONH parameters of the subjects obtained by Cirrus HD-OCT. Average GC-IPL thickness was 89.1 μm in the healthy eyes, and it decreased as the glaucoma severity increased (84.2, 80.8 and 70.9 μm for glaucoma suspect, early glaucoma, and moderate-to-severe glaucoma, respectively), as did the other GC-IPL parameters. There were statistically significant differences in all GC-IPL parameters in the healthy eyes versus glaucoma suspect group and in the early glaucoma versus moderate-to-severe glaucoma group. Furthermore, statistically significant differences were present between the glaucoma suspect and early glaucoma groups in minimum, inferotemporal and inferonasal GC-IPL thicknesses (P=0.009, 0.013, and 0.016). The average RNFL thickness was 105.2 μm in the healthy eyes, and it decreased as the glaucoma severity increased (97.3, 92.7 and 71.7 μm for glaucoma suspect, early glaucoma, and moderate-to-severe glaucoma, respectively). Statistically significant differences between healthy eyes and glaucoma suspect group were detected only for the average and superior RNFL thicknesses (P=0.000 for both). However, there were no significant differences between the glaucoma suspect and early glaucoma groups for all the RNFL parameters, whereas

Table 2 Macular GC-IPL, peripapillary RNFL and ONH parameters obtained by Cirrus HD-OCT mean±SD

Parameters	Healthy eyes (40 eyes)	Glaucoma suspects (40 eyes)	Early glaucoma (40 eyes)	Moderate-to-severe glaucoma (27 eyes)	*P*	P^b	P^c	P^d
GC-IPL thickness								
Min	85.5±6.3	81.1±3.8	77.2±6.9	67.0±9.3	<0.001	0.004	0.009	0.000
Average	89.1±6.3	84.2±4.2	80.8±6.6	70.9±13.3	<0.001	0.001	0.026	0.001
Superonasal	92.0±7.0	86.2±4.3	83.0±7.3	67.3±10.4	<0.001	0.000	0.042	0.000
Superior	88.1±7.2	82.4±4.9	78.9±7.0	67.1±10.1	<0.001	0.001	0.025	0.000
Superotemporal	87.8±6.5	82.9±4.4	79.7±6.7	64.9±12.3	<0.001	0.001	0.074	0.001
Inferotemporal	89.4±6.1	85.2±4.3	81.3±7.5	62.7±10.6	<0.001	0.002	0.013	0.003
Inferior	86.7±7.2	82.4±4.7	78.9±7.0	67.3±10.7	<0.001	0.010	0.026	0.001
Inferonasal	90.6±6.6	85.8±4.7	82.3±6.9	67.0±9.3	<0.001	0.001	0.016	0.002
RNFL thickness								
Average	105.2±8.1	97.3±9.8	92.7±13.1	71.7±13.7	<0.001	0.000	0.181	0.000
Superior	126.5±11.8	110.8±12.7	107.0±18.7	81.9±20.4	<0.001	0.000	0.600	0.000
Inferior	129.3±13.2	123.0±19.8	115.3±22.4	77.8±24.6	<0.001	0.021	0.192	0.000
Temporal[a]	75.7±12.3	72.8±13.1	68.0±11.3	58.6±10.7	<0.001	0.708	0.283	0.011
Nasal[a]	88.0±12.0	82.5±12.8	80.3±14.6	68.6±12.7	<0.001	0.241	0.876	0.003
ONH parameters								
Rim area	1.59±0.25	1.39±0.19	1.28±0.28	0.94±0.37	<0.001	0.000	0.106	0.000
Vertical c/d ratio	0.46±0.14	0.56±0.14	0.63±0.19	0.75±0.15	<0.001	0.000	0.050	0.000
Average c/d ratio	0.49±0.15	0.60±0.15	0.66±0.20	0.74±0.18	<0.001	0.000	0.069	0.001
Cup volume	0.20±0.23	0.33±0.23	0.38±0.26	0.68±0.48	<0.001	0.000	0.317	0.005
Disc area	2.20±0.37	2.31±0.39	2.30±0.46	2.37±0.44	0.263			

GC-IPL: Ganglion cell-inner plexiform layer; RNFL: Retinal nerve fiber layer; ONH: Optic nerve head; SD: Standard deviation. Bonferroni correction $P<0.017$; [a]Parametric test $P<0.05$; [b]*P* values for comparing glaucoma suspect and healthy groups; [c]*P* values for comparing early glaucoma and glaucoma suspect groups; [d]*P* values for comparing moderate-to-severe glaucoma and early glaucoma groups.

there was a significant difference between early glaucoma and moderate-to-severe glaucoma groups for all RNFL thickness measurements. Further, all the ONH parameters, except for the disc area, were significantly different between the healthy eye group and glaucoma suspect group, and moderate-to-severe glaucoma and early glaucoma groups, whereas none of the ONH parameters were significantly different between glaucoma suspects and early glaucoma patients.

The AUCs of discriminating abilities of GC-IPL, RNFL, and ONH parameters between all the consecutive glaucoma stages are shown in Table 3. The best parameters for distinguishing glaucoma suspects from subjects with healthy eyes were superonasal GC-IPL, superior RNFL, and average c/d ratio (AUCs=0.746, 0.810, and 0.746, respectively). While all RNFL and ONH parameters failed to distinguish early glaucoma from glaucoma suspect, minimum, inferotemporal and inferonasal GC-IPL parameters were successful in distinguishing early glaucoma from glaucoma suspect, with the AUCs of 0.669, 0.662, and 0.657, respectively. However, the diagnostic performance of GC-IPL parameters was not as strong as in the other consecutive group comparisons. Moreover, minimum GC-IPL, average RNFL, and rim area (AUCs=0.900, 0.858, 0.768, respectively) were the best parameters for discriminating moderate-to-severe glaucoma group from the early glaucoma group. The ROC curves for the discriminating ability of best GC-IPL, RNFL, and ONH parameters for all the consecutive group comparisons are shown in Figure 1.

DISCUSSION

Glaucoma is a chronic progressive disorder, and its definitive diagnosis should be made as early as possible to prevent vision loss. Despite the advances in diagnostic tools that can quantitatively measure structural damage in the optic nerve, early diagnosis of glaucoma is still challenging. Currently, the detection and follow-up of structural glaucomatous damages are mostly done by focusing on the RNFL and the ONH parameters. However, as glaucoma initially affects RGCs and their axons, measurement of RGC thicknesses along with RNFL thicknesses would help to estimate structural glaucomatous damage more accurately.

The GCA algorithm used in Cirrus HD-OCT was developed to measure the macular GC-IPL thickness. Previous studies have proved the discriminating performance of GC-IPL parameters for distinguishing glaucomatous eyes from healthy eyes; and the diagnostic performance of the GC-IPL parameters was comparable to those of the RNFL, and the ONH parameters[14-15]. In this study, our results demonstrated that macular GC-IPL parameters can discriminate glaucoma suspects from subjects with healthy eyes, and also each of the

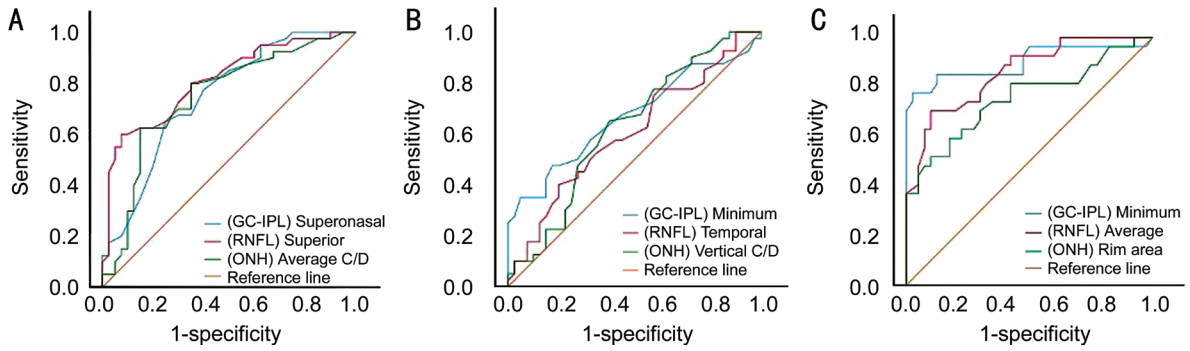

Figure 1 The ROC curves for discriminating performance of the best GC-IPL, RNFL and ONH parameters between glaucoma suspect and normal (A), early glaucoma and glaucoma suspect (B), and moderate-to-severe glaucoma and early glaucoma groups (C).

Table 3 AUC values of GC-IPL, RNFL and ONH parameters for discriminating consecutive glaucoma stages

Parameters	Healthy eyes *vs* glaucoma suspect		Glaucoma suspect *vs* early glaucoma		Early glaucoma *vs* moderate-to-severe glaucoma	
	AUC (95%CI)	*P*	AUC (95%CI)	*P*	AUC (95%CI)	*P*
GC-IPL thickness						
Min	0.688 (0.571-0.806)	0.004	0.669 (0.549-0.789)	0.009	0.900 (0.810-0.990)	0.000
Average	0.725 (0.615-0.834)	0.001	0.645 (0.522-0.767)	0.026	0.880 (0.800-0.960)	0.000
Superonasal	0.746 (0.639-0.853)	0.000	0.632 (0.508-0.755)	0.042	0.781 (0.657-0.906)	0.000
Superior	0.725 (0.615-0.834)	0.001	0.645 (0.524-0.767)	0.025	0.812 (0.702-0.922)	0.000
Superotemporal	0.721 (0.609-0.833)	0.001	0.616 (0.491-0.740)	0.074	0.850 (0.756-0.945)	0.000
Inferotemporal	0.703 (0.589-0.816)	0.002	0.662 (0.540-0.783)	0.013	0.847 (0.750-0.945)	0.000
Inferior	0.666 (0.546-0.786)	0.011	0.644 (0.522-0.767)	0.026	0.883 (0.795-0.971)	0.000
Inferonasal	0.709 (0.597-0.822)	0.001	0.657 (0.536-0.777)	0.016	0.870 (0.784-0.957)	0.000
RNFL thickness						
Average	0.749 (0.641-0.858)	0.000	0.587 (0.461-0.713)	0.181	0.858 (0.769-0.947)	0.000
Superior	0.810 (0.716-0.904)	0.000	0.534 (0.403-0.665)	0.600	0.821 (0.717-0.925)	0.000
Inferior	0.650 (0.527-0.773)	0.021	0.585 (0.459-0.711)	0.192	0.856 (0.759-0.953)	0.000
Temporal	0.579 (0.452-0.706)	0.224	0.604 (0.480-0.728)	0.110	0.719 (0.592-0.845)	0.003
Nasal	0.626 (0.503-0.749)	0.052	0.557 (0.430-0.684)	0.379	0.722 (0.598-0.846)	0.002
ONH parameters						
Rim area	0.736 (0.625-0.847)	0.000	0.606 (0.478-0.735)	0.106	0.768 (0.632-0.881)	0.000
Vertical c/d ratio	0.734 (0.619-0.849)	0.000	0.627 (0.505-0.753)	0.050	0.756 (0.638-0.897)	0.000
Average c/d ratio	0.746 (0.635-0.856)	0.000	0.623 (0.497-0.748)	0.069	0.730 (0.591-0.870)	0.001
Cup volume	0.718 (0.603-0.834)	0.001	0.572 (0.444-0.701)	0.317	0.704 (0.571-0.837)	0.005
Disc area	0.402 (0.276-0.527)	0.130	0.507 (0.378-0.637)	0.912	0.538 (0.398-0.677)	0.605

GC-IPL: Ganglion cell-inner plexiform layer; RNFL: Retinal nerve fiber layer; ONH: Optic nerve head; AUC: Area under the curve.

consecutive stages of glaucoma. It was also shown that, based on the AUC values, the discriminating performance of macular GC-IPL parameters was comparable to that of the RNFL parameters, and the ONH parameters.

There are limited data in the literature on the diagnostic performance of GC-IPL parameters in distinguishing glaucoma suspect eyes or eyes with pre-perimetric glaucoma (PPG) from the healthy eyes[14,16-18]. Furthermore, studies have reported conflicting results on the effectiveness of GC-IPL parameters. In the study of Begum *et al*[16], it was reported that the diagnostic performance of the GC-IPL parameters was similar to that of RNFL and ONH parameters for perimetric glaucoma, whereas the GC-IPL parameters were not statistically different between eyes with PPG and healthy eyes. Moreover, the diagnostic performance of GC-IPL parameters was significantly lower than that of RNFL and ONH parameters for the PPG group. In contrast, Na *et al*[14] reported a significant difference in GC-IPL thicknesses between eyes with PPG and

healthy eyes, which may demonstrate that macular GC-IPL thickness can be used as an early indicator of glaucomatous damage. In addition, Xu *et al*[17] showed that GC-IPL thicknesses, especially the minimum GC-IPL thickness, could distinguish early glaucoma from healthy eyes and glaucoma suspects, with high sensitivity and specificity. In our study, all GC-IPL parameters could successfully distinguish glaucoma suspect eyes from healthy eyes. The AUC values of GC-IPL parameters ranged from 0.666 to 0.746, with the best parameters being the superonasal, superior, and average thicknesses. Although, the best GC-IPL parameter had slightly lower diagnostic performance than that of the best RNFL parameter (superior quadrant, AUC=0.810), it was comparable to that of the ONH parameter (average c/d ratio, AUC=0.746). A possible reason for the difference in the ability of GC-IPL parameters to distinguish glaucoma suspect from normal eyes among the previous studies could be the differences in the ratio of OHT and PPG in the glaucoma suspect group. Moreover, it is speculated that the ethnic differences between the selected patient populations may contribute to these results[16,18].

The usefulness of GC-IPL parameters in discriminating eyes with early glaucoma from the healthy eyes has been reported previously[9,19-20]. Mwanza *et al*[19] evaluated the diagnostic performance of GC-IPL parameters and demonstrated that minimum, inferotemporal, and average GC-IPL thicknesses were the best parameters for discriminating between early glaucoma patients and subjects with healthy eyes; and their performance was comparable to that of the peripapillary RNFL thickness. Jeoung *et al*[9] reported that the best diagnostic parameters for early glaucoma diagnosis were minimum and inferotemporal GC-IPL thickness, average RNFL thickness, and rim area. Similarly, in the report of Nouri-Mahdavi *et al*[21], the best diagnostic GC-IPL parameters were minimum and inferotemporal thicknesses, which were also comparable to the inferior quadrant RNFL thickness. However, in the literature, there are limited data available on discriminating ability of GC-IPL parameters as well as that of the RNFL and the ONH parameters for distinguishing glaucoma suspects from patients at the early glaucoma stage[17,22].

Glaucoma suspect and the early glaucoma classifications are closely related and can often be misdiagnosed. Lack of an accurate glaucoma diagnosis in the early period can cause severe vision loss, while misdiagnosis of a glaucoma suspect as a glaucoma positive can lead to lifelong unnecessary and expensive treatment. In this study, we investigated the usefulness of GC-IPL parameters for distinguishing glaucoma suspects from patients at the early glaucoma stage. Because patients with early glaucoma were compared to glaucoma suspects in this study, the AUCs were lower than that reported by other studies, in most of which the comparisons were made between the early glaucoma group and the normal group. Furthermore, our results have shown that minimum, inferotemporal, and inferonasal GC-IPL parameters discriminated patients with early glaucoma from the glaucoma suspects, whereas no RNFL or ONH parameter was found to be statistically significant for discriminating between the two. The study of Jeoung *et al*[9], has reported that macular GC-IPL parameters generally have higher sensitivities (26.8%-73.2%) than the RNFL parameters (6.1%-61.6%), at comparable specificities for detecting early glaucoma. Also, they speculated that macular GC-IPL parameters might be more accurate than RNFL parameters in the detection of early RGC loss as it typically results in isolated damage in the paracentral areas. Our study also supports the results of the previous studies; the most sensitive parameters for early glaucomatous damage were found to be the minimum and the inferotemporal GC-IPL.

In our study, as expected, the GC-IPL and the RNFL thicknesses were found to be the lowest in the moderate-to-severe glaucoma group, which was in accordance with the nature of the disease. All the GC-IPL, the RNFL, and the ONH parameters were successful in discriminating moderate-to-severe glaucoma from early glaucoma. The best diagnostic GC-IPL parameters were the minimum and the inferior thicknesses (AUC=0.900 and 0.883, respectively). The best RNFL and ONH parameters were average and inferior RNFL thicknesses (AUC=0.858 and 0.856, respectively); rim area and vertical c/d ratio (AUC=0.768 and 0.756, respectively). The AUCs of the best GC-IPL parameters were higher than those of the ONH parameters, whereas they were comparable to those of the RNFL parameters. On the other hand, Mittal *et al*[11] reported that average and superior RNFL thicknesses were more successful than the other parameters in distinguishing early glaucoma from moderate, and advanced glaucoma. Bambo *et al*[23] reported that the inferior macular GC-IPL sectors, minimum GC-IPL thickness, and inferior quadrant RNFL were the best parameters to distinguish the glaucoma severity levels. Also, Jeoung *et al*[9] reported that the best parameters were minimum and inferotemporal GC-IPL (AUC=0.960 and 0.938, respectively), and the average and inferior RNFL (AUC=0.958, for both), and rim area (AUC=0.943) for discriminating moderate-to-severe glaucoma patients. In their study, moderate-to-severe glaucoma was compared to healthy control, making their study different from our study. Therefore, they reported higher AUC values than those of our study. It was hypothesized that minimum GC-IPL thickness measurement might be more accurate than average and sector thickness measurements owing to the focal progression of glaucoma. Moreover, regional variations in vulnerability to glaucomatous damage may be masked by averaging the thickness values obtained in average

or sector parameters[24]. Also, Mwanza *et al*[19] speculated that the central VF is usually preserved until the advanced stage of glaucoma, and thus, the macular GC-IPL may be a parameter that can be used in advanced stage of glaucoma when the ONH and peripapillary RNFL parameters have already reached the lowest measurements. In advanced stages of glaucoma, Belghith *et al*[25] reported that GC-IPL is better than RNFL as a parameter for detecting changes in severely advanced glaucoma. Lavinsky *et al*[26] recently demonstrated a statistically significant rate of progression of GC-IPL (average, superior, and inferior) and rim area, despite the floor effect of the RNFL. These findings are particularly important in terms of progression follow-up in patients with advanced glaucoma, where neural tissue is limited due to the floor effect. However, further studies are required to investigate the value of macular GC-IPL as a follow-up parameter in severe glaucoma.

There are also some limitations of our study. We combined moderate and severe glaucoma groups to form the moderate-to-severe glaucoma group, in order to simplify the comparisons between patients with early glaucoma, and those with more severe glaucomatous damage than that observed in early glaucoma. However, this prevented us from evaluating the ability of GC-IPL parameters for discriminating moderate and severe glaucoma groups. Further, the number of patients in moderate-to-severe glaucoma group was relatively lower than the numbers of patients in other groups. Moreover, the average age of patients in the moderate-to-severe glaucoma group was significantly higher (P=0.044) than that of early glaucoma group, which must be considered while comparing the GC-IPL and the RNFL thicknesses between these groups.

Despite these limitations, we identified that GC-IPL parameters could discriminate glaucoma suspects from subjects with healthy eyes and also all the consecutive stages of glaucoma from each other. Moreover, the discriminating performance of GC-IPL thicknesses was comparable to those of RNFL and ONH parameters. Based on the results obtained in this study, it is believed that GC-IPL parameters can successfully be used in distinguishing consecutive stages of glaucoma. Also, those can be the first parameters that must be followed particularly in distinguishing glaucoma suspect patients from patients with early glaucoma. However, further studies are needed to validate the applicability of this approach in the clinical setting.

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