Jpn J Ophthalmol (2014) 58:244–251
DOI 10.1007/s10384-014-0315-7

THE OFFICIAL INTERNATIONAL JOURNAL OF THE JAPANESE OPHTHALMOLOGICAL SOCIETY

CLINICAL INVESTIGATION

Comparative study of macular ganglion cell complex thickness measured by spectral-domain optical coherence tomography in healthy eyes, eyes with preperimetric glaucoma, and eyes with early glaucoma

Yu Jeong Kim · Min Ho Kang · Hee Yoon Cho · Han Woong Lim · Mincheol Seong

Received: 19 May 2013 / Accepted: 16 January 2014 / Published online: 11 March 2014

Abstract
Purpose To evaluate the diagnostic accuracy of Topcon 3D spectral-domain optical coherence tomography (SD-OCT) for measuring the macular inner retinal layers and the circumpapillary retinal nerve fiber layer (cpRNFL) in order to detect preperimetric glaucoma.
Methods Two hundred four eyes, including 64 healthy eyes, 68 eyes with preperimetric glaucoma, and 72 eyes with early glaucoma were analyzed. Patients had a comprehensive ocular examination including visual field testing and SD-OCT imaging (3D OCT-2000; Topcon Corporation, Tokyo, Japan) in the macular and peripapillary regions. OCT macular scans were segmented into the macular nerve fiber layer (mNFL), ganglion cell layer with the inner plexiform layer (GCIP), and ganglion cell complex (GCC) (composed of the mNFL and GCIP). Ability to discriminate preperimetric glaucoma was assessed using the area under the receiver operating curve for all macular parameters and the cpRNFL.
Results The median visual field MD was -0.78 ± 1.19 dB for the healthy group, -1.02 ± 1.29 dB for the preperimetric glaucoma group, and -3.08 ± 1.61 dB for the early glaucoma group. There were significant differences between the preperimetric and healthy groups for GCIP and GCC and for almost all cpRNFL thickness parameters ($P < 0.05$), except for the mNFL and cpRNFL (nasal, 3, 4, 8, 9, and 10 o'clock sectors). The comparisons among the AUCs of the cpRNFL parameters (0.772), the GCIP parameters (0.727) and the GCC parameters (0.720) showed no significant differences in their abilities to detect preperimetric glaucoma.
Conclusions The capacity of Topcon 3D-OCT macular intraretinal parameters (GCIP and GCC measurements, not mNFL measurements) to diagnose preperimetric glaucoma is similar to that of the cpRNFL.

Keywords Preperimetric glaucoma · Ganglion cell complex · GCC · Retinal nerve fiber layer · RNFL

Introduction

Glaucoma is a progressive optic neuropathy characterized by gradual degeneration of neuronal tissue, in which the retinal ganglion cells (RGCs) are injured, leading to visual field loss. A reduction in retinal nerve fiber layer (RNFL) thickness is an early sign of glaucoma, and a significant reduction in the RGC density can occur before visual field deficits are detected [1, 2]. In fact, approximately 30–50 % of RGCs may be lost before detectable visual field deficits occur [3, 4]. Therefore, it is important to identify the structural changes resulting from RGC loss as early as possible to prevent visual damage. In the presence of normal visual field tests, clinicians may complement their evaluation by ordering additional diagnostic tests, such as an evaluation of the optic nerve or RNFL with quantitative imaging techniques. The results obtained from imaging can assist clinicians in deciding whether preperimetric glaucomatous optic neuropathy is present, and how to proceed with treatment and follow-up.

Optical coherence tomography (OCT) is a noninvasive optical imaging technique that has been used to evaluate in vivo morphologic changes in the optic nerve head, retina, and macular area [5]. The recent introduction of

Y. J. Kim · M. H. Kang · H. Y. Cho · H. W. Lim · M. Seong (✉)
Department of Ophthalmology, Hanyang University College of Medicine, Guri Hospital, Guri, Gyeonggi, Korea
e-mail: goddns76@hanmail.net

spectral-domain optical coherence tomography (SD-OCT) has enhanced the scan resolution and provides better reproducibility for image acquisition than does time-domain OCT [6]. The higher resolution has enabled clinicians to measure the thicknesses of the three inner retinal layers—the nerve fiber, ganglion cell, and inner plexiform layers. Collectively, these layers are known as the ganglion cell complex (GCC) [7].

The primary pathology of glaucoma involves the loss of ganglion cells. About 50 % of RGCs are located in the macula [8]. The parameters originally applied to OCT for glaucoma diagnosis were circumpapillary RNFL (cpRNFL) measurements, but recent studies have demonstrated that GCC thickness also exhibits good glaucoma-detecting ability—comparable to cpRNFL thickness [9–11]. SD-OCT devices are commercially available from several different companies. The speed and resolution of image acquisition vary among the instruments, despite their similar working principles. GCC assessment with Spectralis and Cirrus SD-OCT allowed accurate detection of preperimetric glaucomatous damage in a cohort of glaucoma suspects [12, 13]. However, to our knowledge, no studies have analyzed these macular parameters of preperimetric glaucoma using the Topcon 3D-OCT device.

The purpose of the study described in the present paper was to evaluate the ability of the GCC parameters obtained by Topcon 3D-OCT to discriminate between healthy eyes and those with preperimetric glaucoma or early glaucoma, and then to compare the preperimetric glaucoma diagnostic ability of the GCC parameters with that of the cpRNFL thickness obtained by Topcon 3D-OCT.

Materials and methods

Participants

This retrospective cross-sectional study included 204 eyes of 204 participants: 64 healthy eyes, 68 eyes with preperimetric glaucoma, and 72 eyes with early glaucoma. All participants visited the general health care clinic or glaucoma clinic of the Guri Hanyang University Medical Center from September 2011 through May 2013. The study protocol was approved by the institutional review board of Hanyang University Medical Center and adhered to the tenets of the Declaration of Helsinki.

Each patient underwent a comprehensive ophthalmic examination, including a review of the medical history, best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure measurement using Goldmann applanation tonometry, gonioscopy, dilated funduscopy using a 78-D lens, stereoscopic optic disc photography, and the Humphrey Field Analyzer (HFA) Swedish Interactive Threshold Algorithm (SITA) 30-2 test (Carl Zeiss Meditec, Dublin, CA, USA). All patients underwent more than 1 HFA test. To minimize the learning effect, only the results of the second HFA test were used in the analysis. The HFAs were considered reliable when the fixation losses were <20 %, and false-positive and false-negative errors were <15 %. A normal visual field was defined as a mean deviation and pattern standard deviation within 95 % confidence limits and a glaucoma hemifield test result within normal limits. Eyes with glaucomatous visual field defects were defined as those with a cluster of 3 points with probabilities of <5 % on the pattern deviation map in at least 1 hemifield, including at least 1 point with a probability of <1 %; or a cluster of 2 points with a probability of <1 %, and a glaucoma hemifield test (GHT) result outside 99 % of age-specific normal limits or a pattern standard deviation (PSD) outside 95 % of normal limits.

To be included, patients had to have a best-corrected visual acuity of at least 20/40, spherical refraction $<\pm 6.0$ D, cylinder correction <3.0 D, and an open angle with gonioscopy. Patients with coexisting retinal disease, uveitis, or nonglaucomatous optic disc neuropathy were excluded from the study. Poor-quality OCT images such as those with low signal strength (<70), motion artifact, or decentration were excluded.

Healthy eyes were defined as those of patients with no first-degree relatives with glaucoma, no history or evidence of intraocular surgery, IOP <22 mmHg, a normal optic disc appearance, and normal ophthalmologic findings. The preperimetric glaucoma group patients met the same criteria for optic nerve head and NFL changes as did the perimetric glaucoma group patients (typical neuroretinal rim loss or notching as judged by slit-lamp biomicroscopy, focal thinning of the NFL, disc hemorrhages, or vertical elongation of the optic cup), but they did not demonstrate visual field loss. Early glaucoma was defined as eyes with visual field loss with an MD ≥ -6 dB. When both eyes of a patient were eligible, one eye was randomly selected, and the cpRNFL measurement was presented with right eye orientation.

Instrumentation

The 3D OCT-2000 (software version 8.0; Topcon Corporation, Tokyo, Japan) was used to obtain measurements of RNFL thickness and the posterior pole of the eye.

For the 3D-OCT, a 7 × 7-mm scan disc protocol was used. Images with a quality factor of >70 were used for the analyses. RNFL thickness data with 1024 points of resolution on a 3.46-mm circle diameter were exported by the software provided by Topcon Corporation and evaluated as described below.

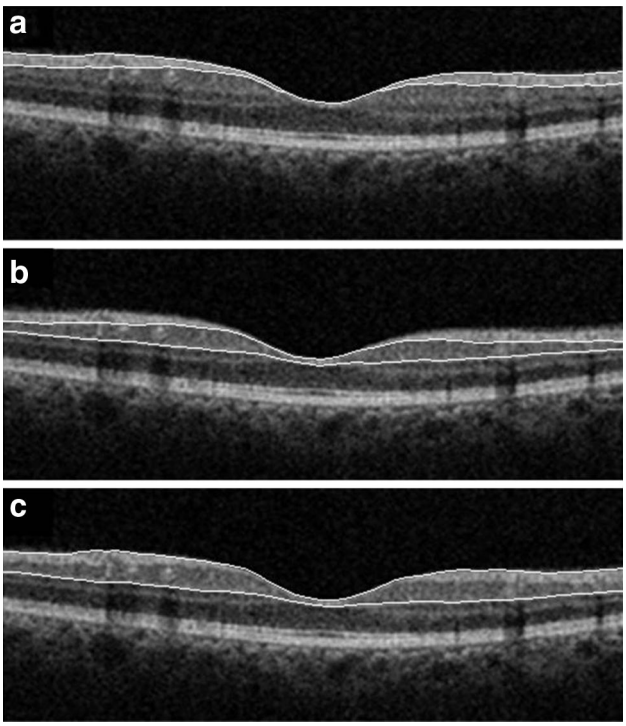

Fig. 1 Topcon 3D-OCT cross-sectional image through the fovea. The three lines correspond to the internal limiting membrane (ILM), the boundary between the nerve fiber layer (NFL) and the ganglion cell layer (GCL), and the boundary line between the inner nuclear layer (INL) and the inner plexiform layer (IPL). **a** Macular NFL (mNFL: from the ILM to the outer boundary of the RNFL); **b** ganglion cell layer with inner plexiform layer (GCIP: from the outer boundary of the RNFL to the outer boundary of the IPL); **c** ganglion cell complex (GCC: from the ILM to the outer boundary of the IPL; combination of the RNFL and the GCIP)

Raster scanning of a 7-mm^2 area centered on the fovea with a scan density of 512 (vertical) × 128 (horizontal) scans was performed using 3D-OCT. The built-in 3D-OCT measured a 6 × 6-mm area that was centered on the fovea using the embedded 3D-OCT measurement software. The data, divided into 10 × 10 grids, were exported by the software provided by Topcon Corporation. The average and superior and inferior hemiretina thicknesses of the mNFL, GCL/IPL, and GCC were calculated.

The 3D OCT-2000 built-in software automatically generated three boundary lines between the retinal layers by using a threshold algorithm that searches for changes in reflectivity. These boundary lines delineated the internal limiting membrane (ILM), the boundary between the nNFL and the ganglion cell layer (GCL), and the boundary between the inner nuclear layer (INL) and the inner plexiform layer (IPL) (Fig. 1). These boundary lines were used to measure the thicknesses of the macular NFL (mNFL) and the GCL with the IPL (GCIP), as well as the GCC (composed of the mNFL and GCIP). The algorithm identifies the mNFL layer (from the ILM to the boundary of the RNFL), the GCIP (from the outer boundary of the RNFL to the outer boundary of the IPL; a combination of the RGC layer and the IPL), and the GCC (from the ILM to the outer boundary of the IPL; a combination of the RNFL and the GCIP).

Statistical analysis

Statistically analyses were performed using IBM SPSS Statistics version 17 software (SPSS, Chicago, IL, USA). The thicknesses of the GCC and cpRNFL parameters of the healthy eyes were compared with those of the eyes with preperimetric glaucoma and early glaucoma by one-way ANOVA. ANOVA and the Tukey test for multiple comparisons were used to compare the findings between groups. The ROC curves were used to assess the abilities of the GCC and cpRNFL parameters to detect preperimetric glaucoma. Probability values of <0.05 were considered to indicate significance.

Results

Patients

We studied 204 eyes: 64 healthy eyes, 68 eyes with preperimetric glaucoma, and 72 eyes with early glaucoma. The patient demographics are presented in Table 1. Among the three groups, the differences in age, IOPs, and refractive errors were not significant, but the differences in the MD and PSD were ($P < 0.001$ for both).

Circumpapillary RNFL thicknesses in the three groups

Table 2 shows the mean thicknesses of the cpRNFLs (clock-hour, quadrant, and average RNFL) in the three groups. All parameters decreased from normal to preperimetric glaucoma and from preperimetric glaucoma to early glaucoma. Almost all clock-hour, quadrant, and average RNFL thicknesses were significantly thinner in the patients with preperimetric glaucoma than in the healthy participants, but the nasal, 3, 4, 8, 9, and 10 o'clock thicknesses were not. Patients with early glaucoma had significantly thinner RNFL than did the healthy participants in almost all of the peripapillary sectors ($P < 0.05$ for all values except the 9 o'clock sector).

Ganglion cell complex thickness in the three groups

Table 3 shows the mean thickness of the GCC parameter measurements (mNFL, GCIP, and GCC) for the healthy eyes, eyes with preperimetric glaucoma, and eyes with early glaucoma in the superior, inferior, and average sectors. All parameters were observed to decrease from normal to preperimetric glaucoma and from preperimetric

Table 1 Demographic characteristics of the study groups

	Healthy	Preperimetric glaucoma	Early glaucoma	*P* value		
				N vs PG	PG vs EG	EG vs N
Age (years)	51.77 ± 14.44	53.12 ± 10.69	56.83 ± 12.73	0.814	0.198	0.055
IOP (mmHg)	13.94 ± 2.47	13.78 ± 3.46	13.90 ± 2.95	0.951	0.968	0.997
SE (D)	−0.85 ± 2.74	−0.78 ± 2.11	−0.91 ± 2.37	0.983	0.944	0.989
MD (dB)	−0.78 ± 1.19	−1.02 ± 1.29	−3.08 ± 1.61	0.613	<0.001*	<0.001†
PSD (dB)	1.71 ± 0.60	1.87 ± 0.50	4.29 ± 2.64	0.850	<0.001*	<0.001†

Data are expressed as means ± SDs

N normal, *PG* preperimetric glaucoma, *EG* early glaucoma, *IOP* intraocular pressure, *SE* spherical equivalent, *MD* mean deviation, *PSD* pattern standard deviation

* Post hoc least significant difference tests demonstrated that the preperimetric glaucoma group differed from the early glaucoma group ($P = 0.000$)

† Post hoc least significant difference tests demonstrated that the healthy group differed from the early glaucoma group ($P = 0.000$)

Table 2 Comparison of circumpapillary RNFL thickness among the three groups by one-way ANOVA

	cpRNFL			*P* value		
	Healthy	Preperimetric glaucoma	Early glaucoma	N vs PG	PG vs EG	EG vs N
Average	111.20 ± 9.25	99.87 ± 11.92	89.47 ± 14.03	<0.001*	<0.001†	<0.001‡
Temporal	85.74 ± 13.06	78.57 ± 14.72	70.89 ± 14.38	0.011*	0.004†	<0.001‡
Superior	131.48 ± 19.73	116.73 ± 16.96	103.78 ± 22.89	<0.001*	0.001†	<0.001‡
Nasal	89.92 ± 13.93	84.83 ± 14.50	80.51 ± 15.62	0.119	0.195	0.001‡
Inferior	137.55 ± 18.63	120.73 ± 17.18	102.05 ± 20.05	<0.001*	<0.001†	<0.001‡
3	71.82 ± 15.93	66.37 ± 14.93	61.15 ± 13.52	0.088	0.095	<0.001‡
2	100.55 ± 20.36	90.07 ± 18.82	80.20 ± 20.61	0.008*	<0.001†	0.011‡
1	134.94 ± 18.19	120.64 ± 21.98	102.80 ± 29.33	0.002*	<0.001†	<0.001‡
12	124.69 ± 19.82	112.57 ± 20.20	101.69 ± 27.86	0.006*	0.012†	<0.001‡
11	130.20 ± 18.11	117.00 ± 20.83	107.15 ± 25.01	0.002*	0.021†	<0.001‡
10	104.81 ± 19.80	98.66 ± 19.75	90.02 ± 20.55	0.185	0.031†	<0.001‡
9	77.11 ± 14.57	74.75 ± 15.74	71.06 ± 17.36	0.676	0.360	0.073
8	87.96 ± 16.08	83.70 ± 15.53	80.51 ± 18.35	0.313	0.499	0.028‡
7	122.40 ± 16.96	107.68 ± 19.11	100.36 ± 21.40	<0.001*	0.067	<0.001‡
6	164.82 ± 21.95	126.87 ± 24.55	110.01 ± 25.25	<0.001*	0.009†	<0.001‡
5	150.73 ± 20.70	125.13 ± 26.69	96.08 ± 29.00	<0.001*	<0.001†	<0.001‡
4	85.25 ± 15.06	79.16 ± 17.98	70.02 ± 17.54	0.100	0.005†	<0.001‡

Data are expressed as means ± SDs

N normal, *PG* preperimetric glaucoma, *EG* early glaucoma, *cpRNFL* circumpapillary RNFL

* Significant difference between healthy and preperimetric glaucoma

† Significant difference between preperimetric glaucoma and early glaucoma

‡ Significant difference between healthy and early glaucoma

glaucoma to early glaucoma. The values of the GCIP and GCC parameters differed significantly among the healthy eyes, the eyes with preperimetric glaucoma, and those with early glaucoma ($P < 0.001$). However, the mNFL thickness did not significantly differ between the healthy eyes and those with preperimetric glaucoma (average $P = 0.068$; superior $P = 0.292$; inferior $P = 0.066$).

AUCs of the three segmented macular layers and cpRNFL thickness

The AUCs of the cpRNFL, mNFL, GCIP, and GCC parameters for detecting preperimetirc glaucoma are presented in Table 4. A comparison of the healthy and preperimetric groups showed that the two largest area under the receiver operating curve (AUROC) values were those for the average cpRNFL thickness (0.772) and the inferior cpRNFL thickness (0.780). The comparison of the AUCs of the average cpRNFL (0.772), GCIP (0.727), and GCC (0.720) parameters showed no significant differences in the ability to detect preperimetric glaucoma ($P = 0.3328$, 0.2801). The AUC of the average mNFL thickness was inferior to those of the average cpRNFL, GCIP, and GCC thicknesses (0.641 vs 0.772, 0.727, 0.720; $P = 0.0197$, 0.0717, 0.0052, respectively). Figure 2 shows the ROC curves for the mNFL, GCIP, GCC, and average cpRNFL thicknesses obtained with Topcon 3D-OCT.

Table 3 Comparison of the macula inner retina thicknesses of the three groups with one-way ANOVA

	Macular inner retina thickness			*P* value		
	Healthy	Preperimetric glaucoma	Early glaucoma	N vs PG	PG vs EG	EG vs N
mNFL						
Average	36.32 ± 3.75	34.37 ± 4.82	29.06 ± 6.06	0.068	<0.001†	<0.001‡
Superior	34.81 ± 3.93	33.33 ± 5.52	30.49 ± 6.94	0.292	0.009†	<0.001‡
Inferior	37.89 ± 4.38	35.39 ± 5.10	27.31 ± 8.59	0.066	<0.001†	<0.001‡
GCIP						
Average	70.49 ± 5.04	66.49 ± 5.36	62.36 ± 6.55	<0.001*	<0.001†	<0.001‡
Superior	71.57 ± 5.37	67.74 ± 6.00	64.96 ± 7.67	0.002*	0.032†	<0.001‡
Inferior	69.49 ± 5.15	65.24 ± 5.46	59.88 ± 6.80	<0.001*	<0.001†	<0.001‡
GCC						
Average	107.22 ± 8.07	100.53 ± 9.17	91.24 ± 10.98	<0.001*	<0.001†	<0.001‡
Superior	106.68 ± 8.40	100.72 ± 10.531	95.57 ± 13.59	0.007*	0.019†	<0.001‡
Inferior	107.83 ± 8.48	100.35 ± 9.29	86.99 ± 13.59	<0.001*	<0.001†	<0.001‡

Data are expressed as means ± SDs

N normal, *PG* preperimetric glaucoma, *EG* early glaucoma, *MNFL* macular nerve fiber layer, *GCIP* ganglion cell layer with inner plexiform layer, *GCC* ganglion cell complex

* Significant difference between healthy and preperimetric glaucoma

† Significant difference between preperimetric glaucoma and early glaucoma

‡ Significant difference between healthy and early glaucoma

Table 4 Comparison between the areas under the receiver operating characteristic curves and sensitivities and specificities for discriminating between the preperimetric glaucoma and healthy groups

	Healthy vs PG	95 % CI		*P* value	Sensitivity	Specificity
		Lower bound	Upper bound			
cpRNFL						
Average	0.772 (0.04)	0.691	0.841	<0.0001	61.8	89.1
Temporal	0.644 (0.05)	0.556	0.726	0.0029	39.7	90.6
Superior	0.730 (0.04)	0.645	0.803	<0.0001	67.6	73.4
Nasal	0.597 (0.05)	0.508	0.681	0.0513	60.3	60.9
Inferior	0.780 (0.04)	0.700	0.848	<0.0001	80.9	67.2
Macular inner retina thickness						
mNFL						
Average	0.641 (0.05)	0.553	0.723	0.0034	58.8	67.2
Superior	0.607 (0.05)	0.518	0.691	0.0316	27.9	96.9
Inferior	0.647 (0.05)	0.559	0.728	0.0022	45.6	82.8
GCIP						
Average	0.727 (0.04)	0.643	0.801	<0.0001	61.8	78.1
Superior	0.696 (0.05)	0.610	0.773	<0.0001	58.8	78.1
Inferior	0.738 (0.04)	0.655	0.811	<0.0001	61.8	82.8
GCC						
Average	0.720 (0.04)	0.635	0.794	<0.0001	66.2	73.4
Superior	0.684 (0.05)	0.597	0.762	0.0001	63.2	73.4
Inferior	0.746 (0.04)	0.663	0.817	<0.0001	55.9	87.5

PG preperimetric glaucoma, *cpRNFL* circumpapillary RNFL, *MNFL* macular nerve fiber layer, *GCIP* ganglion cell layer with inner plexiform layer, *GCC* ganglion cell complex

Discussion

Loss of RGCs and RNFL thinning have been shown to precede the development of a glaucomatous visual field defect [14–19]. Thus, the detection of early structural changes may be crucial to making a timely diagnosis [16–19]. It is important to decide whether preperimetric glaucomatous optic neuropathy is present when establishing treatment and follow-up plans.

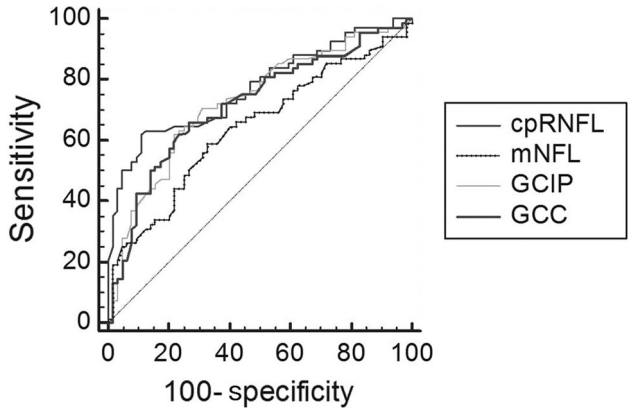

Fig. 2 Comparison of receiver operating characteristic (ROC) curves created using the average thicknesses of the mNFL, GCIP, GCC, and cpRNFL

About 50 % of RGCs are located in the macula [8]. The primary pathology of glaucoma involves the loss of ganglion cells, with the highest RGC density found in the macula. Therefore, RGC loss should theoretically be easiest to detect in the macular region, making the evaluation of this region useful in the diagnosis of glaucoma. Evaluation of macular thickness has received increasing attention since Ziemer et al. [20] hypothesized that retinal thickness mapping can be used to detect early glaucomatous damage and to monitor the progression of glaucoma. Several studies have shown that macular thickness allows the detection of glaucomatous damage [21–28]. However, macular measurements did not have a higher predictive value than cpRNFL thickness values [20–22, 25, 29, 30]. Leung et al. [22] reported that cpRNFL thickness parameters were better than measurements of macular thickness for diagnosing glaucoma.

However, Zeimer et al. [20] assessed the total macular thickness rather than that of the RGC layer, thus decreasing the specificity of the macular thickness for glaucoma diagnosis. Glaucoma primarily affects the axons and cell bodies of the RGCs, which constitute the inner retina. The axons, cell bodies, and dendrites of RGCs are believed to reside in the RNFL, GCL, and IPL, respectively [23]. Therefore, to detect glaucomatous change, it may be more accurate to measure the thicknesses of these specific layers rather than the total macular thickness [31]. The diagnostic ability of the SD-OCT macular parameters indicates that the ganglion cell complex (GCC) thickness—composed of the three innermost retinal layers (the NFL, RGC layer, and IPL)—offers higher diagnostic power than the total macular thickness for differentiating between healthy and perimetric glaucoma eyes [9, 32], and similar diagnostic power to that of cpRNFL thickness [10, 31–34]. Arintawati et al. [35] reported that the macular GCC and RNFL thickness parameters obtained by RTVue SD-OCT were able to differentiate preperimetric and perimetric glaucomatous eyes from healthy eyes.

Our results showed significant differences between the preperimetric and healthy groups for the GCIP and GCC and for almost all cpRNFL thickness parameters except for the mNFL and cpRNFL thicknesses (nasal, 3, 4, 8, 9, and 10 o'clock sectors). Furthermore, the GCC and cpRNFL thicknesses decreased from normal to preperimetric glaucoma and from preperimetric glaucoma to early glaucoma. Our study showed that MIRL (GCIP and GCC scan, but not mNFL) thickness analysis had a similar ability to discriminate between eyes with preperimetric glaucoma and controls to cpRNFL analysis.

Our study showed that 3D-OCT thickness measurements of the inner retinal layers in the macula have comparable preperimetric glaucoma diagnostic abilities with and without inclusion of the mNFL, and a similar diagnostic ability to cpRNFL thickness measurements. However, mNFL thickness underperformed compared to the cpRNFL, GCIP, and GCC thicknesses. Na et al. [13] reported that the mNFL thickness did not differ significantly between healthy and preperimetric glaucoma eyes. They suggested that the reason for this lack of a significant difference was the distribution and thickness of the NFL. The NFL is thickest in the superior and inferior peripapillary areas and gradually becomes thinner as the distance from the disc margin increases. The macular scan of their study covered 6 × 6 mm of the retina, with the fovea used as the center. A certain proportion of the peripapillary RNFL bundle running outside the 6 × 6-mm field of the macular scan was not included in the macular measurements. Therefore, the mNFL thickness underperformed only the cpRNFL, GCIP, and GCC thicknesses in detecting preperimetric glaucoma.

Kotowski et al. [36] showed that the SD-OCT thickness of the macula inner retinal layers has comparable glaucoma diagnostic ability with and without the inclusion of the mNFL, and is similar to that of the cpRNFL thickness. However, in these studies, the differences were significant only for patients with perimetric glaucoma. No significant differences were detected when comparing the healthy eyes with those with preperimetric glaucoma. These results differed from the findings of our study, most likely because the definition of preperimetric glaucoma differed between the two studies. Kotowski et al. defined glaucoma suspect in individuals with ocular hypertension and/or optic nerve head changes in the presence of a full visual field. We defined preperimetric glaucoma as the presence of glaucomatous changes observed in disc photographs or of RNFL thinning observed in red-free photographs. We accepted typical glaucomatous changes only. Therefore, we may have included patients with glaucomatous changes

of higher severity. The MD value of the visual field supported this hypothesis. This severe criterion for preperimetric glaucoma might have affected our results.

We know that localized RNFL defects in glaucoma are most often found in the inferotemporal and superotemporal sectors and are rarely seen in the nasal fundus region. However, our study showed that patients with early glaucoma had significantly thinner RNFL in the nasal area than did normal participants. We thought that this was because we included some generalized concentric atrophic discs. Generalized concentric disc atrophy may sometimes enlarge the cup horizontally and cause diffuse RNFL thinning. In addition, other previous studies did not completely follow the rule that we stated above [33, 37]. Therefore, it may be that cpRNFL thinning occurred in the nasal fundus.

The limitations of this study include the use of a homogeneous population. Data from a single ethnic group may not be applicable to other groups. Furthermore, we did not discriminate between normal-tension and high-tension glaucoma. Also, the relatively small sample size of each group may have limited the discriminating power of our subgroup analysis.

In conclusion, Topcon 3D-OCT macular intraretinal parameters offer preperimetric glaucoma diagnostic ability comparable to that of cpRNFL thickness. The exclusion of the mNFL did not change the diagnostic ability of the inner retinal measurements. Therefore, the assessment of GCIP and GCC thicknesses measured by Topcon 3D-OCT may be a good alternative to cpRNFL thickness assessment for the detection of glaucoma. These findings are useful when cpRNFL measurements may be unreliable, especially in eyes with unusually small or large optic discs, peripapillary atrophy, or a tilted optic disc. The ability to use cpRNFL and/or macula measurements might further enhance the utility of OCT in preperimetric glaucoma detection.

Acknowledgments This work was supported by a research fund from Hanyang University (HY-2012).

Conflicts of interest Y. J. Kim, None; M. H. Kang, None; H. Y. Cho, None; H. W. Lim, None; M. Seong, None.

References

1. Ajtony C, Balla Z, Somoskeoy S, Kovacs B. Relationship between visual field sensitivity and retinal nerve fiber layer thickness as measured by optical coherence tomography. Invest Ophthalmol Vis Sci. 2007;48:258–63.
2. Asrani S, Challa P, Herndon L, Lee P, Stinnett S, Allingham RR. Correlation among retinal thickness, optic disc, and visual field in glaucoma patients and suspects: a pilot study. J Glaucoma. 2003;12:119–28.
3. Quigley HA, Addicks EM, Green WR. Optic nerve damage in human glaucoma. III. Quantitative correlation of nerve fiber loss and visual field defect in glaucoma, ischemic neuropathy, papilledema, and toxic neuropathy. Arch Ophthalmol. 1982;100:135–46.
4. Mikelberg FS, Yidegiligne HM, Schulzer M. Optic nerve axon count and axon diameter in patients with ocular hypertension and normal visual fields. Ophthalmology. 1995;102:342–8.
5. Rao HL, Zangwill LM, Weinreb RN, Sample PA, Alencar LM, Medeiros FA. Comparison of different spectral domain optical coherence tomography scanning areas for glaucoma diagnosis. Ophthalmology. 2010;117:1692–9.
6. Kim JS, Ishikawa H, Sung KR, et al. Retinal nerve fibre layer thickness measurement reproducibility improved with spectral domain optical coherence tomography. Br J Ophthalmol. 2009; 93:1057–63.
7. Kim NR, Lee ES, Seong GJ, Kim JH, An HG, Kim CY. Structure–function relationship and diagnostic value of macular ganglion cell complex measurement using Fourier-domain OCT in glaucoma. Invest Ophthalmol Vis Sci. 2010;51:4646–51.
8. Curcio CA, Allen KA. Topography of ganglion cells in human retina. J Comp Neurol. 1990;300:5–25.
9. Tan O, Chopra V, Lu AT, Schuman JS, Ishikawa H, Wollstein G, et al. Detection of macular ganglion cell loss in glaucoma by Fourier-domain optical coherence tomography. Ophthalmology. 2009;116:2305-14e1–2.
10. Schulze A, Lamparter J, Pfeiffer N, Berisha F, Schmidtmann I, Hoffmann EM. Diagnostic ability of retinal ganglion cell complex, retinal nerve fiber layer, and optic nerve head measurements by Fourier-domain optical coherence tomography. Graefes Arch Clin Exp Ophthalmol. 2011;249:1039–45.
11. Garas A, Vargha P, Hollo G. Diagnostic accuracy of nerve fibre layer, macular thickness and optic disc measurements made with the RTVue-100 optical coherence tomograph to detect glaucoma. Eye (Lond). 2011;25:57–65.
12. Lisboa R, Leite MT, Zangwill LM, Tafreshi A, Weinreb RN, Medeiros FA. Diagnosing preperimetric glaucoma with spectral domain optical coherence tomography. Ophthalmology. 2012;119:2261–9.
13. Na JH, Sung KR, Baek S, Kim YJ, Durbin MK, Lee HJ, et al. Detection of glaucoma progression by assessment of segmented macular thickness data obtained using spectral domain optical coherence tomography. Invest Ophthalmol Vis Sci. 2012; 53:3817–26.
14. Hoyt WF, Frisen L, Newman NM. Funduscopy of nerve fiber layer defects in glaucoma. Invest Ophthalmol. 1973;12:814–29.
15. Quigley HA, Miller NR, George T. Clinical evaluation of nerve fiber layer atrophy as an indicator of glaucomatous optic nerve damage. Arch Ophthalmol. 1980;98:1564–71.
16. Sommer A, Katz J, Quigley HA, Miller NR, Robin AL, Richter RC, et al. Clinically detectable nerve fiber atrophy precedes the onset of glaucomatous field loss. Arch Ophthalmol. 1991;109:77–83.
17. Quigley HA, Katz J, Derick RJ, Gilbert D, Sommer A. An evaluation of optic disc and nerve fiber layer examination in monitoring progression of early glaucoma damage. Ophthalmology. 1992;99:19–28.
18. Airaksinen PJ, Drance SM, Douglas GR, Mawson DK, Nieminen H. Diffuse and localized nerve fiber loss in glaucoma. Am J Ophthalmol. 1984;98:566–71.
19. Harwerth RS, Carter-Dawson L, Shen F, Smith EL III, Crawford ML. Ganglion cell losses underlying visual field defects from experimental glaucoma. Invest Ophthalmol Vis Sci. 1999;40:2242–50.
20. Zeimer R, Asrani S, Zou S, Quigley H, Jampel H. Quantitative detection of glaucomatous damage at the posterior pole by retinal thickness mapping. Ophthalmology. 1998;105:224–31.
21. Ojima T, Tanabe T, Hangai M, Yu S, Morishita S, Yoshimura N. Measurement of retinal nerve fiber layer thickness and macular

volume for glaucoma detection using optical coherence tomography. Jpn J Ophthalmol. 2007;51:197–203.
22. Leung CK, Chan WM, Yung WH, Ng AC, Woo J, Tsang MK, et al. Comparison of macular and peripapillary measurements for the detection of glaucoma: an optical coherence tomography study. Ophthalmology. 2005;112:391–400.
23. Tan O, Li G, Lu AT, Varma R, Huang D. Mapping of macular substructures with optical coherence tomography for glaucoma diagnosis. Ophthalmology. 2008;115:949–56.
24. Ishikawa H, Stein DM, Wollstein G, Beaton S, Fujimoto JG, Schuman JS. Macular segmentation with optical coherence tomography. Invest Ophthalmol Vis Sci. 2005;46:2012–7.
25. Greenfield DS, Bagga H, Knighton RW. Macular thickness changes in glaucomatous optic neuropathy detected using optical coherence tomography. Arch Ophthalmol. 2003;121:41–6.
26. Koseki N, Araie M, Suzuki Y, Yamagami J. Visual field damage proximal to fixation in normal- and high-tension glaucoma eyes. Jpn J Ophthalmol. 1995;39:274–83.
27. Araie M, Yamagami J, Suziki Y. Visual field defects in normal-tension and high-tension glaucoma. Ophthalmology. 1993;100: 1808–14.
28. Weber J, Dannheim F, Dannheim D. The topographical relationship between optic disc and visual field in glaucoma. Acta Ophthalmol (Copenh). 1990;68:568–74.
29. Wollstein G, Schuman JS, Price LL, Aydin A, Beaton SA, Stark PC, et al. Optical coherence tomography (OCT) macular and peripapillary retinal nerve fiber layer measurements and automated visual fields. Am J Ophthalmol. 2004;138:218–25.
30. Medeiros FA, Zangwill LM, Bowd C, Vessani RM, Susanna R Jr, Weinreb RN. Evaluation of retinal nerve fiber layer, optic nerve head, and macular thickness measurements for glaucoma detection using optical coherence tomography. Am J Ophthalmol. 2005;139:44–55.
31. Seong M, Sung KR, Choi EH, Kang SY, Cho JW, Um TW, et al. Macular and peripapillary retinal nerve fiber layer measurements by spectral domain optical coherence tomography in normal-tension glaucoma. Invest Ophthalmol Vis Sci. 2012;51:1446–52.
32. Mori S, Hangai M, Sakamoto A, Yoshimura N. Spectral-domain optical coherence tomography measurement of macular volume for diagnosing glaucoma. J Glaucoma. 2010;19:528–34.
33. Nakatani Y, Higashide T, Ohkubo S, Takeda H, Sugiyama K. Evaluation of macular thickness and peripapillary retinal nerve fiber layer thickness for detection of early glaucoma using spectral domain optical coherence tomography. J Glaucoma. 2011;20:252–9.
34. Girkin CA, Liebmann J, Fingeret M, Greenfield DS, Medeiros F. The effects of race, optic disc area, age, and disease severity on the diagnostic performance of spectral-domain optical coherence tomography. Invest Ophthalmol Vis Sci. 2011;52:6148–53.
35. Arintawati P, Sone T, Akita T, Tanaka J, Kiuchi Y. The applicability of ganglion cell complex parameters determined from SD-OCT images to detect glaucomatous eyes. J Glaucoma. 2012;22:713–8.
36. Kotowski J, Folio LS, Wollstein G, Ishikawa H, Ling Y, Bilonick RA, et al. Glaucoma discrimination of segmented cirrus spectral domain optical coherence tomography (SD-OCT) macular scans. Br J Ophthalmol. 2012;96:1420–5.
37. Nouri-Mahdavi K, Nikkhou K, Hoffman DC, Law SK, Caprioli J. Detection of early glaucoma with optical coherence tomography (StratusOCT). J Glaucoma. 2008;17:183–8.