Rates of Ganglion Cell-Inner Plexiform Layer Thinning in Normal, Open-Angle Glaucoma and Pseudoexfoliation Glaucoma Eyes: A Trend-Based Analysis

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Purpose. The purpose of this study was to determine the rate of ganglion cell–inner plexiform layer (GCIPL) thinning by Cirrus high-definition optical coherence tomography (HD-OCT) in normal eyes and open-angle glaucoma (OAG) and pseudoexfoliation glaucoma (PXG) eyes.

Methods. This was a longitudinal observational study. We evaluated 282 subjects who visited a glaucoma clinic of a tertiary hospital in Korea: 60 healthy eyes, 193 medically treated OAG eyes, and 29 medically treated PXG eyes with a minimum 3-year follow-up involving serial spectral-domain OCT measurement of GCIPL thickness. The rates of thinning in the GCIPL thickness of the global region, six macular sectors, and minimum thickness were determined by linear mixed model and compared among the normal, OAG, and PXG groups. Additionally, the GCIPL thinning rates were compared between normal-baseline-IOP OAG (normal-tension glaucoma [NTG]) and high-baseline-IOP OAG (high-tension glaucoma [HTG]) eyes.

Results. The mean rates of GCIPL thinning were −0.31 μm/y in the normal eyes, −0.49 μm/y in OAG, and −1.46 μm/y in PXG. The differences in the mean GCIPL thinning rates were statistically significant between OAG and PXG (normal versus OAG, $P = 0.231$; OAG versus PXG, $P < 0.001$; normal versus PXG, $P < 0.001$). Among the eyes with OAG, the treated NTG and HTG eyes showed no significant difference in GCIPL thinning rate (NTG versus HTG = −0.41 μm/y versus −0.66 μm/y, $P = 0.123$).

Conclusions. We determined the GCIPL thinning rates for normal and undertreated OAG and PXG eyes. Differences existed among the normal eyes and glaucoma types, with PXG progressing significantly faster than OAG.

Keywords: ganglion cell-inner plexiform layer, open-angle glaucoma, pseudoexfoliation glaucoma, trend-based analysis

During the last few decades, optical coherence tomography (OCT) has been widely used for monitoring glaucomatous patients and for detecting structural progression using quantitative measurement.[1–4] Using the commercially available OCT devices and embedded software, assessment of progressive changes usually focuses on the evaluation of the optic disc and retinal nerve fiber layer (RNFL) based on event-analysis and/or trend-analysis.[3] Recently, the value of assessing the macular inner retinal structure, including the ganglion cell-inner plexiform layer (GCIPL) or ganglion cell complex (GCC), for diagnosing glaucoma has been the focus of many studies, and these have demonstrated that those parameters show better or comparable glaucoma diagnostic performances to the RNFL parameters.[5–8] A previous study performed by our group reported that trend-based analysis for calculation of GCIPL thinning rate using Cirrus OCT showed good diagnostic performance in detecting glaucoma progression.[9] More recently, automated guided progression analysis (GPA) software has become available for serial GCIPL measurement; already, one study on GCIPL GPA has been published.[10] However, in those studies, the GCIPL thinning rate between progressors and nonprogressors was evaluated only among open-angle glaucoma (OAG) patients; no normal individuals were included. Several newer studies have evaluated the rate of macular GCIPL or GCC change in normal individuals and compared them with glaucoma patients using trend-based analysis.[11–13] However, no study has yet compared the GCIPL thinning rate between normal eyes and OAG and PXG, and neither has any study compared OAG as divided into normal-baseline-IOP OAG (normal-tension glaucoma [NTG]) and high-baseline-IOP OAG (high-tension glaucoma [HTG]) eyes.

The purpose of the present study was to compare the rates of change in GCIPL thickness, as measured by SD-OCT, in normal, OAG, and PXG eyes. Using trend-based analysis, we evaluated the diagnostic performance of the GCIPL thinning rate in detecting OAG and compared the GCIPL thinning rates between the NTG and HTG OAG groups.

Materials and Methods

This study was approved by the Institutional Review Board of Seoul National University Hospital with informed consent

obtained. The study design followed the tenets of the Declaration of Helsinki for biomedical research.

Subjects

A total of 282 subjects; 60 normal subjects, 193 OAG patients, and 29 PXG patients were enrolled and followed-up for at least 36 months at the Department of Ophthalmology of Seoul National University Hospital, from October 2012 to September 2016. The subjects were enrolled in the Macular Ganglion Cell Imaging Study, an ongoing study designed in 2011. All subjects underwent a complete ophthalmologic examination, including visual acuity tests, manifest refraction assessment, slit-lamp examination, IOP measurements using Goldmann applanation tonometry, gonioscopy, dilated fundus examination, color disc photography, red-free RNFL photography (TRC-50IX; Topcon Corporation, Tokyo, Japan), Swedish interactive thresholding algorithm (SITA) 30-2 perimetry (Humphrey field analyzer II; Carl Zeiss Meditec, Jena, Germany), and Cirrus HD-OCT (Carl Zeiss Meditec, Inc., Dublin, CA, USA). The inclusion criteria were age between 20 and 79 years, best-corrected visual acuity of $\geq$20/40 in the study eye, a refractive error within $\pm$6.00 diopters (D) equivalent sphere, and $\pm$3.00 D astigmatism.

Patients with a history of surgical therapy, such as glaucoma filtering surgery in the study eye, were excluded. However, patients who underwent only cataract surgery were not excluded. Patients with any other ocular disease that could interfere with visual function or any media opacity that would significantly interfere with OCT image acquisition were excluded as well. Patients with any other macular disease that could interfere with segmentation of retinal layers were excluded. Patients also were excluded if no high-quality image could be obtained (i.e., if all of the OCT images showed a signal strength $<$ 6).

Patients with OAG were identified by the presence of glaucomatous optic disc changes with corresponding glaucomatous visual field (VF) defects and an open angle confirmed by gonioscopic examination ($>$180° visible pigmented posterior trabecular meshwork on nonindentation gonioscopy in primary position). Glaucomatous optic disc changes were defined as neuroretinal rim thinning, notching, excavation, or RNFL defects. Glaucomatous VF defects were defined as (1) glaucoma hemifield test values outside the normal limits, (2) three or more abnormal points with a probability of being normal of $P < 5\%$, of which at least one point has a pattern deviation of $P < 1\%$, or (3) a pattern standard deviation of $P < 5\%$. The VF defects were confirmed on two consecutive reliable tests (fixation loss rate $\leq$ 20%, false-positive and false-negative error rates $\leq$ 25%). In this study, OAG was defined above, without the presence of exfoliation in the dilated pupil. OAG in this study means primary OAG. On the basis of baseline IOP (measured at the time of subject's first visit), patients with OAG were divided into two groups in subanalysis: NTG (baseline IOP $<$ 21 mm Hg) and HTG (baseline IOP $\geq$ 21 mm Hg). PXG in this study was defined additionally to OAG as concomitant with the presence of exfoliation material, a grayish-white material, observed at the anterior lens capsule and/or at the pupillary border with a dilated pupil. All of the glaucoma patients were treated for glaucoma at the discretion of the attending ophthalmologist (KHP), who aimed to reduce baseline IOP by at least 20%. When this was not accomplished, further treatment decisions were made by the treating physician. Patients who needed additional surgical treatment during the follow-up were excluded from this study. Normal individuals were defined as patients with no history or evidence of intraocular surgery except cataract surgery, IOP $\leq$ 21 mm Hg with no history of increased IOP, the absence of glaucomatous disc appearance, and normal ophthalmologic findings.

All the patients underwent regular follow-up visits 6 months apart, at which time they underwent clinical examination, color disc photography, and red-free RNFL photography. Both eyes were imaged with Cirrus HD-OCT and were examined by standard automated perimetry (SAP) every 6 to 12 months for $\geq$36 months. For cases in which both eyes met all of the eligibility criteria, one eye was randomly chosen as the study eye prior to the analyses.

Calculation of Cirrus HD-OCT GCIPL and RNFL Thickness Thinning Rates

Methodologic details on the calculation of thinning rates have been described previously,[11,14] and we modified the method. In brief, the linear mixed model analysis was performed for GCIPL or RNFL thickness to determine the rate of change in thickness (expressed in micrometers per year). Images with a signal strength $<$6, those that did not focus on the fovea, and cases of algorithm segmentation failure were excluded from the linear mixed model analysis.

Statistical Analyses

The rate of GCIPL or RNFL changes from baseline was determined from the serial OCT measurements using linear mixed model analysis. Models were fitted with fixed coefficient (fixed effects) of age, sex, systemic factors (diabetes mellitus, hypertension), group (normal, OAG [NTG and HTG], and PXG), spherical equivalent refractive error, central corneal thickness, baseline VF mean deviation (MD), baseline VF pattern standard deviation (PSD), mean VF index, baseline IOP, mean follow-up IOP, baseline GCIPL thickness, baseline RNFL thickness, time, and the interaction term group $\times$ time. The rate of changes was compared among groups through testing of the interaction term in the linear mixed models.

$P < 0.05$ was considered statistically significant. All statistical tests were performed using IBM SPSS Statistics 24 (SPSS, Chicago, IL, USA).

Results

The study involved 60 eyes of normal subjects, 193 eyes of OAG, and 29 eyes of PXG subjects who had fulfilled the inclusion criteria for this study. Table 1 shows the clinical demographics of all patients at the time of enrollment. Between the normal and OAG groups, the differences in age, average IOP, average number of GCIPL OCT scans, and follow-up periods were not significant, although those in baseline IOP, MD, PSD, VF index, baseline GCIPL, and RNFL thicknesses were. Between the normal and PXG groups, the differences in age, baseline IOP, average IOP, MD, PSD, VF index, OCT scan number, follow-up period, baseline GCIPL, and RNFL thickness were significant ($P < 0.05$).

Comparison of GCIPL Thinning Rate Between Normal Eyes and Glaucoma

Table 2 and the Figure show a comparison of the rates of GCIPL and RNFL thinning between normal eyes and glaucoma. The rate of change for global GCIPL was –0.31 ($P = 0.021$), –0.49 ($P < 0.001$), and –1.46 μm/y ($P = 0.004$) in the normal, OAG, and PXG groups, respectively (Table 2; Fig.; $P < 0.001$ for all between-group comparisons). The distributions of the global GCIPL and RNFL thinning rates of each of the groups are presented in the Figure. The global GCIPL thinning rate was faster in OAG than in normal subjects, but it was not statistically significant ($P = 0.231$). The GCIPL thinning rate

Table 1. Clinical Demographic Characteristics of Enrolled Patients

	Normal ($N = 60$)	OAG ($N = 193$)	PXG ($N = 29$)	*P* Value			
				P Value*	N vs. OAG	OAG vs. PXG	N vs. PXG
Age (y)	51.7 ± 12.7	54.9 ± 12.1	67.3 ± 8.3	<0.001	0.170	<0.001	<0.001
Sex (male)	32 (53.3)	101 (52.3)	16 (55.2)	0.956			
Diabetes	7 (11.7)	22 (11.4)	7 (24.1)	0.153			
Hypertension	9 (15.0)	38 (19.7)	19 (65.5.)	<0.001	0.415	<0.001	<0.001
Baseline IOP (mm Hg)	13.5 ± 2.4	17.3 ± 5.2	19.3 ± 8.0	<0.001	<0.001	0.177	<0.001
Average IOP (mm Hg)	12.6 ± 1.8	13.0 ± 2.7	14.3 ± 2.8	0.010	0.564	0.024	0.008
CCT (μm)	549.5 ± 36.0	541.3 ± 35.5	536.3 ± 30.6	0.285			
Medications (no.)†	0.0 ± 0.1	1.9 ± 1.1	2.4 ± 1.0	<0.001	<0.001	0.026	<0.001
SE (D)	−2.06 ± 2.65	−2.39 ± 3.38	−1.38 ± 2.09	0.432			
Axial length (mm)	25.0 ± 1.6	24.6 ± 1.6	24.3 ± 1.6	0.452			
MD (dB)	−0.88 ± 1.95	−5.69 ± 6.34	−6.53 ± 6.68	<0.001	<0.001	0.743	<0.001
PSD (dB)	2.10 ± 0.76	6.70 ± 4.82	5.88 ± 3.27	<0.001	<0.001	0.584	<0.001
VF index (%)	98.7 ± 1.6	84.3 ± 20.2	87.4 ± 19.0	<0.001	<0.001	1.000	0.002
OCT scan number	4.4 ± 0.9	4.4 ± 0.8	3.8 ± 0.7	0.001	0.969	0.001	0.002
Follow-up period (mo)	48.2 ± 8.1	44.9 ± 9.8	42.5 ± 13.6	0.022	0.062	0.459	0.032
Baseline GCIPL (μm)	80.1 ± 6.3	69.8 ± 8.8	68.4 ± 7.8	<0.001	<0.001	0.674	<0.001
Baseline RNFL (μm)	89.7 ± 10.2	74.0 ± 12.0	72.8 ± 11.6	<0.001	<0.001	0.861	<0.001

CCT, central corneal thickness.

* Comparisons were performed by χ^2 test for categorical variables and by 1-way ANOVA for continuous variables. Also, a Tukey multiple comparison test was performed for postprocessing.

† Medication at the time of study enrollment.

was significantly faster in PXG than in OAG globally ($P < 0.001$), in the superior hemifields ($P = 0.005$), and in the SN and IN sectors ($P < 0.001$ and $P < 0.001$, respectively). The GCIPL thinning rate was significantly faster in PXG than in normal eyes for almost all GCIPL parameters.

Comparison of GCIPL Thinning Rate Between NTG and HTG

The clinical demographics of the NTG and HTG patients at the time of enrollment are presented in Supplementary Table S1. The GCIPL thinning rates of NTG and HTG were –0.41 μm/y ($P < 0.001$) and –0.66 μm/y ($P < 0.001$), respectively. There was no significant difference between the groups ($P = 0.123$; Supplementary Table S2; Supplementary Fig. S1).

Discussion

In this study, we found that in undertreated OAG eyes, the rate of GCIPL thinning, as measured using Cirrus OCT, was faster than that of in normal subjects, but the difference was not statistically significant. In addition, the GCIPL thinning rate in PXG eyes was significantly faster than that in OAG eyes. It is

Table 2. GCIPL Thinning Rates in Normal Individuals and Patients With Open-Angle Glaucoma

	Normal ($N = 60$)	OAG ($N = 193$)	PXG ($N = 29$)	*P* Value			
				P Value*	N vs. OAG	OAG vs. PXG	N vs. PXG
GCIPL thinning rate (by linear mixed model)							
Average	−0.31 ($P = 0.021$)	−0.49 ($P < 0.001$)	−1.46 ($P = 0.004$)	<0.001	0.231	<0.001	<0.001
Minimum	−0.33 ($P = 0.352$)	−0.90 ($P < 0.001$)	−2.38 ($P = 0.007$)	0.001	0.060	0.002	<0.001
Superior Hemifield	−0.27 ($P = 0.074$)	−0.44 ($P < 0.001$)	−1.26 ($P = 0.003$)	0.006	0.278	0.005	0.002
Inferior Hemifield	−0.29 ($P = 0.039$)	−0.30 ($P = 0.234$)	−1.53 ($P = 0.017$)	0.290	0.987	0.119	0.160
SN	−0.23 ($P = 0.356$)	−0.44 ($P < 0.001$)	−2.52 ($P = 0.001$)	<0.001	0.334	<0.001	<0.001
S	−0.40 ($P = 0.041$)	−0.43 ($P < 0.001$)	−0.64 ($P = 0.158$)	0.080	0.847	0.747	0.690
ST	−0.19 ($P = 0.157$)	−0.46 ($P < 0.001$)	−0.78 ($P = 0.020$)	0.063	0.081	0.177	0.029
IT	−0.22 ($P = 0.231$)	−0.57 ($P < 0.001$)	−0.88 ($P = 0.156$)	0.105	0.072	0.370	0.071
I	−0.46 ($P = 0.044$)	0.10 ($P = 0.882$)	−1.25 ($P = 0.014$)	0.736	0.690	0.473	0.681
IN	−0.12 ($P = 0.510$)	−0.44 ($P < 0.001$)	−2.21 ($P = 0.005$)	<0.001	0.169	<0.001	<0.001
RNFL thinning rate (by linear mixed model)							
Average	−0.60 ($P < 0.001$)	−0.90 ($P < 0.001$)	−1.31 ($P < 0.001$)	0.182	0.118	0.434	0.115
Superior	−1.28 ($P < 0.001$)	−1.17 ($P < 0.001$)	−2.14 ($P = 0.001$)	0.274	0.841	0.108	0.179
Inferior	−1.27 ($P < 0.001$)	−1.46 ($P < 0.001$)	−1.91 ($P < 0.001$)	0.662	0.514	0.586	0.393
Visual field changing rate (by linear mixed model)							
MD	0.18 ($P = 0.017$)	−0.17 ($P = 0.007$)	−0.79 ($P = 0.012$)	<0.001	0.015	0.001	<0.001
PSD	−0.00 ($P = 0.934$)	0.02 ($P = 0.535$)	0.28 ($P = 0.194$)	0.042	0.967	0.041	0.057
VF index	−0.12 ($P = 0.090$)	−0.91 ($P < 0.001$)	−3.14 ($P < 0.001$)	<0.001	0.044	<0.001	<0.001

I, inferior sector; IT, inferotemporal sector; S, superior sector; SN, superonasal sector; ST, superotemporal sector.

* Comparisons among three groups were performed by linear mixed model.

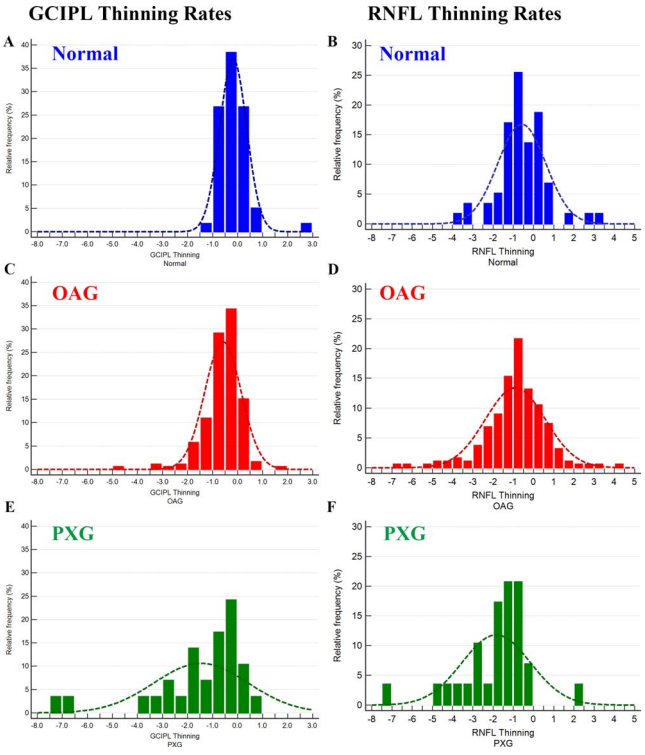

Figure. Rates of GCIPL and RNFL thinning in (**A**, **B**) normal individuals and patients with (**C**, **D**) OAG and (**E**, **F**) PXG.

important to note that there was continued thinning of GCIPL in glaucoma patients who were considered clinically controlled (if they were indeed). Among the OAG eyes, there was no significant difference in GCIPL thinning rates between undertreatment NTG and undertreatment HTG. To our knowledge, this is the first study to compare GCIPL thinning rates among normal, OAG, and PXG eyes and between NTG and HTG using trend-based analysis.

There have been a few trend-based analyses evaluating thinning rates of macular inner retinal thickness in glaucoma patients. Using stratus OCT, Medeiros et al. evaluated the changes in RNFL and macular thickness for detection of progressive structural damage in glaucoma.[15] Sung and Na evaluated macular thickness or volume changes in glaucoma patients using Cirrus OCT to identify glaucoma progression.[16,17]

With the evolution of SD-OCT, segmentation of the retinal layer became possible, and a number of studies evaluating GCIPL thinning rates were performed (Table 3). Leung et al. reported that age-related GCIPL thinning in a normal population was –0.318 µm/y, which was similar to those of normal eyes in our study.[13] This similarity might be due to the enrolled subjects' racial similarity, as the majority of enrolled normal subjects of both studies were East Asian. Recently, Hammel et al. conducted a study similar to ours, evaluating GCIPL thinning rates with Cirrus OCT in both normal and glaucoma eyes.[11] However, there are important interstudy differences. First, in the study of Hammel et al., most of the subjects were of European and African descent, whereas the subjects of our study were East Asian (Korean). The GCIPL thinning rates of normal subjects were slightly different between the two studies (Hammel et al. versus this study: –0.14 vs. –0.31). The rates could have been affected by racial difference. Second, we compared the GCIPL thinning rate of PXG with those of OAG and normal subjects and performed a subanalysis by dividing OAG into NTG and HTG eyes. Interestingly, even in

Table 3. Comparison With Other Studies Evaluating GCIPL Thinning Rates

Study (First Author)	SD-OCT	Racial Distribution (Country)	Groups	FU Duration	GCIPL Thinning Rate (µm/y)		
					Normal	OAG	PXG
2013 Leung[13]	Cirrus	Unknown (Hong Kong)	Age-related GCIPL thinning	45.8 months	–0.318	–0.810	
2016 Belghith[18]	Spectralis	DIGS and ADAGES (United States)	Normal vs. advanced OAG	2.8/3.5 years	–0.11	–0.18	
2016 Hollo[12]	RTVue-XR	Unknown (Hungary)	Normal, OHT, OAG	51.5/6.5/5.0 years	–0.53 (GCC)	–0.80 (GCC)	
2017 Hammel[11]	Cirrus	DIGS (United States) (European 61%/ African 29%)	Normal vs. OAG (mild/mod/severe)	1.7/3.2 years	–0.14	–0.57	
2017 Lee[9]	Cirrus	Asian (Korea)	OAG (nonprogressor vs. progressor)	37.7 months		–0.50 (–0.28 vs. –0.82)	
2017 Shin[10]	Cirrus	Asian (Korea)	OAG (non-progressor vs. progressor)	5 years		–0.53 (–0.40 vs. –0.92)	
2017 Na[14]	Cirrus	Asian (Korea)	OAG (non-DH vs. DH)	51.1/50.1 months		–0.32 vs. –0.78	
2019 Our study	Cirrus	Asian (Korea)	Normal vs. OAG (NTG vs. HTG) vs. PXG	48.2/44.9/42.5 months	–0.31	–0.49 (–0.41 vs. –0.66)	–1.46

ADAGES, African Descent and Glaucoma Evaluation Study; DH, disc hemorrhage; DIGS, Diagnostic Innovations in Glaucoma Study; FU, follow-up; OHT, ocular hypertension; SD-OCT, spectral-domain OCT.

an East Asian population with a high proportion of NTG among OAG, the GCIPL thinning rates of OAG were similar to those of the Western cohort of Hammel et al. (Hammel et al. versus this study: –0.57 vs. –0.49 μm/y).

There have been several other studies that have evaluated the thinning rates of glaucoma patients' inner retinal structures using other SD-OCT devices (Table 3). Using the software developed for the Spectralis machine, Belghith et al. reported GCIPL thinning rates of –0.11 μm/y for normal subjects and –0.18 μm/y for cases of advanced glaucoma.[18] The above-noted GCIPL thinning rates were slightly slower than those of our study, and it could be due to the different segmentation algorithm of SD-OCT equipment. Hollo et al. reported GCC thinning rates in normal, ocular hypertensive, and glaucoma eyes by Avanti RTVue-XR OCT.[12] Although direct comparison with our study might not be appropriate, due to the differences in OCT machines and calculating layers, this study showed, similar to our results, that there was no significant difference in the rates of GCC thinning between the normal and glaucoma eyes.

Undertreated OAG and normal groups showed a difference in the rates of structural change, but it was not statistically significant. There was no significant difference in the average IOP during the follow up between the two groups. This may imply that if the OAG group has been well treated and IOP has been lowered adequately, the rate of structural thinning may have been slowed to the level of the normal group.

Because of the high proportion of NTG in our study population, we investigated, via subanalysis, the difference in the GCIPL thinning rates between NTG and HTG. Unlike the expected results, there was no significant difference between the two groups. There is a possibility that a rate difference was masked due to both groups having been treated with topical medication. It should also be noted that the patients who had had to undergo surgical treatment due to rapid disease progression were not included in this study, which might have influenced the results. From another perspective, NTG and HTG were classified by arbitrary cutoff points (IOP of 21 mm Hg), and therefore it is possible that the absence of any rate difference reflected the fact that those two diseases are in a continuous spectrum.

In our study, the GCIPL thinning rate of PXG was significantly faster than those of normal eyes and nonexfoliative OAG. To our knowledge, this is the first attempt to compare GCIPL thinning rates between PXG and OAG. The rate of VF in PXG was also faster than that of the OAG group. Our results are consistent with those of a previous study analyzing the natural courses of several types of OAG, which consistency suggests that the rate of functional progression is faster in PXG than in OAG.[19] In our study, average IOPs during the follow-up period were higher in PXG than OAG. The difference in GCIPL thinning rates can be caused by this reason, clinicians should treat PXG more aggressively for lowering the IOP.

Several points need to be considered when interpreting the results of the current study. First, we were unable to evaluate the pure natural history of the untreated disease, because we enrolled only treated patients and excluded those who had undergone a follow-up period surgical intervention. Second, macular comorbidities may play a role in influencing the segmentation of GCIPL scans and can limit the ability to directly generalize results and measurements established in this study into actual glaucoma clinic populations. Third, all glaucoma stages were grouped together. This can make the results of the study less significant. Fourth, we did not divide the undertreatment glaucoma patients into progressor and nonprogressor groups and did not evaluate the relationship between GCIPL thinning rates and visual field progression rates. Fifth, subjects enrolled in our study were more myopic compared with previous studies. Myopia can significantly affect GCIPL thickness profiles. As the globe elongated in myopic eyes, the larger retinal surface area results in a decreasing GCIPL thickness.[20] Further studies will be necessary to adequately address these issues.

In conclusion, we evaluated the GCIPL thinning rates for normal, OAG, and PXG eyes in a longitudinal observational study. Differences in GCIPL thinning rate existed among the normal, OAG, and PXG eyes, with PXG progressing significantly faster than OAG.

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