Prelamina and Lamina Cribrosa in Glaucoma Patients With Unilateral Visual Field Loss

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Submitted: October 19, 2015
Accepted: February 22, 2016

Citation: Kim DW, Jeoung JW, Kim YW, et al. Prelamina and lamina cribrosa in glaucoma patients with unilateral visual field loss. *Invest Ophthalmol Vis Sci*. 2016;57:1662–1670. DOI:10.1167/iovs.15-18453

Purpose. To investigate the characteristics of the prelamina and lamina cribrosa (LC) of both eyes in glaucoma patients with unilateral visual field (VF) defect.

Methods. Forty-one subjects diagnosed with primary open-angle glaucoma with unilateral VF loss and 41 age-matched healthy control subjects were scanned by swept-source optical coherence tomography (SS-OCT). All eyes were divided into three groups: VF-affected glaucomatous eyes (group A, $n = 41$), perimetrically unaffected fellow eyes (group B, $n = 41$), and healthy control eyes (group C, $n = 41$). The anterior prelaminar depth (APLD) and LC depth (LCD) were measured at the center of the reference line (the Bruch's membrane opening plane). The prelaminar tissue thickness (PTT) was obtained by subtracting the APLD from the LCD. The APLD, LCD, and PTT were compared among these groups.

Results. The APLD and LCD were significantly greater in group A than in the other groups (group B, $P < 0.001$; group C, $P < 0.001$).The prelaminar tissue was significantly thinner in group A than in the other groups (group B, $P = 0.007$; group C, $P < 0.001$). Also, the prelaminar tissue was significantly thinner in group B than in group C ($P = 0.003$). Multivariate analysis demonstrated a significant association between PTT and initial IOP among the overall study population ($P < 0.05$).

Conclusions. In the fellow eyes with unilateral glaucoma patients, APLD was significantly greater, and the prelaminar tissue was significantly thinner, than in the healthy control eyes. Our findings suggest that subclinical or preperimetric changes of the LC and/or prelaminar tissue are already present in the fellow eyes with unilateral glaucoma.

Keywords: glaucoma, lamina cribrosa, prelaminar tissue, swept source optical coherence tomography

Glaucoma, manifesting as the loss of retinal ganglion cell and axon, is one of the most common causes of blindness in the world. The axonal loss is presumed to initiate at the level of the lamina cribrosa (LC), a multilayered collagenous sieve-like structure at the optic nerve head (ONH) that provides structural and nutritional support to the retinal ganglion cell axons.[1–7] This glaucomatous damage results in optic disc cupping, a distinctive change in the structure of the ONH. Optic nerve head cupping can be divided into two parts: the prelaminar component and the LC component.[2,8,9] The prelaminar component entails progressive prelaminar neural tissue loss, which increases cup depth and width, thus also increasing the cup-to-disc ratio. The laminar component involves the connective tissue, causing progressive posterior movement of the LC and excavation beneath the anterior scleral canal.[3] Glaucomatous cupping most commonly is a result of the changes in both prelaminar and laminar components; it incurs laminar connective tissue damage and remodeling, as well as progressive axonal loss of retinal ganglion cells.[10–12]

Recent advancements in optical coherence tomography (OCT) have facilitated imaging of the deep layers of the ONH, including the LC and sclera. Swept-source OCT (SS-OCT) especially, has a longer central wavelength, so that it offers better tissue penetration compared with conventional spectral-domain OCT (SD-OCT) instruments.[8,13] Several SS-OCT studies assessing the LC have shown promising results.[8,9,14]

In routine clinical practice, patients with unilateral open-angle glaucoma affecting only one eye are frequently encountered. Given that primary open-angle glaucoma (POAG) is generally considered to be a bilateral disease, it is reasonable to postulate that fellow eyes might exhibit (though the time frame will sometimes be asymmetric) subclinical glaucomatous change. However, to the best of our knowledge, this issue has not been completely elucidated. The purpose of the present study was to investigate the characteristics of the prelamina and LC of both eyes in glaucoma patients with unilateral visual field (VF) defect.

Methods

This investigation was based on the *S*wept-*S*ource *O*ptical *C*oherence *T*omography *S*tudy of *L*amina *C*ribrosa (*SOS-LC*), an

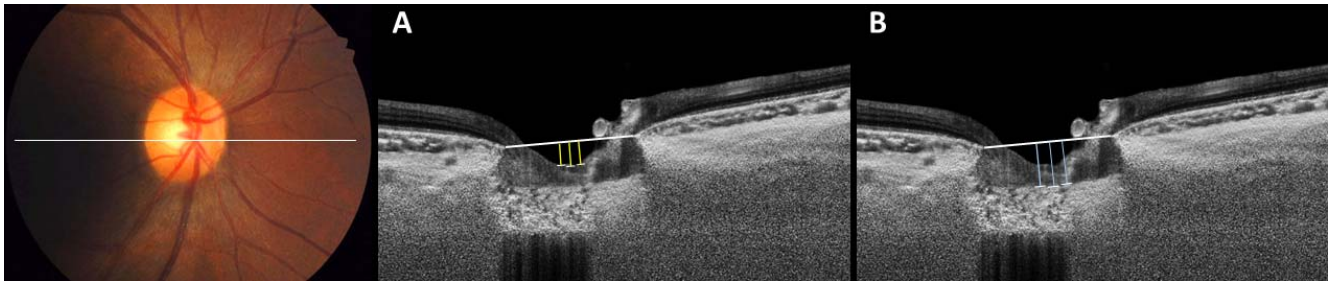

FIGURE 1. Swept-source optical coherence tomography images of prelamina and anterior lamina. At the center of the ONH, the reference line (*white horizontal line*) connects the BMOs. From a perpendicular line drawn from the center of the reference line, APLD (**A**) and LCD (**B**) were measured. Also, two additional points were used for the APLD and LCD measurements. The anterior prelaminar depth was the distance (*yellow vertical line*) from the center of the reference line to the anterior prelaminar surface. The laminar cribrosa depth was the distance (*blue vertical line*) from the center of the reference line to the anterior laminar surface. The prelaminar tissue thickness was the difference between the APLD and the LCD.

ongoing prospective study at Seoul National University Hospital (SNUH). Approved by the Seoul National University Hospital Institutional Review Board, it followed the tenets of the Declaration of Helsinki (1964). Informed consent was given by all patients.

Participants

The *SOS-LC*'s enrolled subjects underwent a full ophthalmic evaluation including the following: best-corrected visual acuity (BCVA) measurement, slit-lamp biomicroscopy, gonioscopy, Goldmann applanation tonometry, dilated fundus examination, optic discstereophotography, red-free retinal nerve fiber layer (RNFL) photography by digital fundus camera (VX-10; Kowa Optimed, Tokyo, Japan), Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA, USA), and standard automated perimetry (30-2 Swedish Interactive Threshold Algorithm standard program; Humphrey Visual Field Analyzer; Carl Zeiss Meditec). The central corneal thickness (Pocket II; Quantel Medical, Clermont-Ferrand, France) and axial length (AXIS-II Ultrasonic Biometer; Quantel Medical S.A., Bozeman, MT, USA) were measured. Also, SS-OCT at full pupil dilation was performed by experienced ophthalmologists.

The patients and subjects were followed up on every 3 to 6 months. Intraocular pressure was measured by Goldmann applanation tonometry on every visit. Regular optic disc stereophotography and red-free RNFL photography, Cirrus HD-OCT, and VF testing, as well as optic disc scanning by SS-OCT, were performed at intervals of 6 months to 1 year.

The SOS-LC inclusion criteria were age 20 $\sim$ 79, BCVA $\geq$ 20/40 in the study eye, spherical refraction $-8.0 \sim +3.0$ diopters, and ± 3.00 D astigmatism. The exclusion criteria were as follows: comorbidity with anterior ischemic optic neuropathy, optic disc drusen, retinal disease (e.g., macular degeneration, diabetic retinopathy, retinal vein occlusion) or brain disease (e.g., pituitary tumor), history of ocular surgery including glaucoma surgery, lack of high-quality (i.e., quality score 15) imaging, ocular fixation issues (with consequent inability to follow the imaging protocol), or cases with diseases causing unilateral high IOP, such as exfoliation syndrome and glaucomatocyclitic crisis.

For inclusion in the present study, patients had to have POAG with unilateral VF loss. In the course of diagnosis, specifically, glaucoma patients with VF defect in one eye and normal VF in the fellow eye were included in this study. Glaucomatous eyes were defined according to the following criteria: the presence of glaucomatous optic disc change such as focal notching and thinning; RNFL defect on disc stereophotography and red free fundus photography; glaucomatous VF defect; and open angle confirmed by gonioscopic examination. The glaucomatous VF defect criteria were (1) a beyond-normal-limit score on the glaucoma hemifield test, or (2) $P < 0.05$ probability of three or more abnormal points, one or more of which with $P < 0.01$ pattern standard deviation, or (3) $P < 0.05$ pattern standard deviation. Two consecutive reliable tests (fixation loss rate $\leq$ 20%, false-positive and false-negative error rates $\leq$ 25%) were considered to represent confirmation of VF defect.

The age-matched healthy individuals were those who had visited the SNUH outpatient clinic for regular ocular check-ups (e.g., dry eye, cataract) and shown no RNFL defect on disc stereophotography, red-free fundus photography, and standard automated perimetry. All eyes were divided into three groups: VF-affected glaucomatous eyes (group A, $n = 41$), perimetrically unaffected fellow eyes (group B, $n = 41$), and healthy control eyes (group C, $n = 41$). One randomly selected eye from each of the normal subjects was included in a healthy control eye group.

Swept-Source Optical Coherence Tomography

The Deep Range Imaging (DRI) SS-OCT system (Topcon Medical Systems, Oakland, NJ, USA) operates at 100,000 Hz A scan repetition rate using a light source of 1050 nm wavelength-sweeping laser, and provides an axial resolution of 8 μm in tissue. A 20-μm transverse resolution was applied in the current study, enabling acquisition of a 1000 A line OCT image in 10 microseconds. Six-millimeter (6-mm) five-line raster scans of the ONH with 0.25-mm spacing between the cross-lines were obtained for each participant. A total of 32 single images were registered and overlapped to create multiaveraged single image.

Measurement of Prelaminar Tissue Thickness (PTT) and LC Depth (LCD)

All of the parameters were measured perpendicularly from the reference line that connected the Bruch's membrane openings (BMOs). The visibility of the LC configuration on all of the scan images was restored by adaptive compensation according to protocols published elsewhere.[15–17] For each of the B-scans, the anterior prelaminar depth (APLD; distance from reference line to anterior prelaminar tissue surface) and the LC depth (LCD) were measured at the center of the reference line. Two points located 100 μm from the center of the reference line temporally and nasally, respectively, also were measured. These three measurements from the three points were averaged, and the result was considered as the APLD (Fig. 1A) or LCD (Fig. 1B) of each selected B-scan. The LCD is the distance from the reference

Table 1. Comparison of Baseline Parameters of Glaucomatous Eyes With VF Loss (Group A), Perimetrically Unaffected Fellow Eyes (Group B), and Healthy Control Eyes (Group C)

	Group A	Group B	Group C	*P* Value$_{A-B}$*	*P* Value$_{A-C}$†	*P* Value$_{B-C}$†
No. of eyes	41	41	41			
Age, y	56.71 ± 1.64	56.71 ± 1.64	58.00 ± 2.66		0.597	0.597
Male sex, %	48.78	48.78	46.34		1.000	1.000
Central corneal thickness, μm	532.59 ± 6.53	539.79 ± 6.88	548.93 ± 8.00	0.086	0.211	0.387
Spherical equivalent	−1.75 ± 3.00	−1.67 ± 3.00	−1.30 ± 2.76	0.607	0.581	0.648
Axial length, mm	24.24 ± 0.21	24.18 ± 0.20	22.56 ± 1.55	0.170	0.183	0.197
Initial IOP, mm Hg	16.7 ± 1.02	15.4 ± 0.47	15.1 ± 0.43	0.207	0.152	0.613
IOP during follow-up, mm Hg	12.6 ± 0.35	13.5 ± 0.31	13.9 ± 0.49	0.001	0.041	0.523
Average CD ratio	0.73 ± 0.01	0.68 ± 0.01	0.67 ± 0.02	<0.001	<0.001	0.578
Vertical CD ratio	0.74 ± 0.01	0.65 ± 0.01	0.63 ± 0.02	<0.001	<0.001	0.329
Optic disc rim area	0.88 ± 0.03	1.01 ± 0.03	1.10 ± 0.04	<0.001	<0.001	0.018
Optic disc size	1.98 ± 0.07	1.93 ± 0.06	2.14 ± 0.10	0.191	0.128	0.059
Optic disc cup volume	0.45 ± 0.04	0.37 ± 0.03	0.39 ± 0.07	0.200	0.301	0.689
MD, dB	−4.66 ± 0.99	−1.20 ± 0.47	−1.30 ± 0.31	<0.001	0.006	0.858

Data are mean ± standard error unless otherwise indicated. CD, cup-to-disc.
* Paired *t*-test.
† Independent *t*-test.
‡ χ^2 test.

line to the anterior laminar tissue surface. The prelaminar tissue thickness (PTT) is the distance between the APLD and the LCD. It was obtained by subtracting the APLD from the LCD. Two observers (D.W.K., Y.W.K.) measured the APLD, LCD, and PTT in the masked fashion.

Reproducibility of Measurements

The intrarater and interrater reproducibility values were evaluated in terms of the intraclass correlation coefficient (ICC) and 95% confidence intervals (CIs), respectively. The intrarater reproducibility evaluation proceeded by repeated measurement of the same scans per rater, and the interrater reproducibility by measurement of the same scans between the raters. According to Fleiss, ICC scores >0.75, 0.40 to 0.75, and <0.4 are considered to be excellent, moderate, and poor, respectively.[18]

Statistical Analysis

A statistical analysis was performed using SPSS software (version 21.0; SPSS, Chicago, IL, USA). The independent *t*-test and paired *t*-test were used to compare the data among the groups. The associations between the PTT and various factors were analyzed using mixed-model univariate and multivariate analyses, in which the independent variables were age, sex, central corneal thickness, spherical equivalent, axial length, initial IOP, mean IOP during follow-up, average and vertical cup-to-disc ratio, optic disc rim area, optic disc size, optic disc cup volume, mean RNFL thickness, and VF mean deviation (MD). The variables that showed significance at $P < 0.05$ were included in the multivariate model. The Pearson correlation analysis was performed to assess the strength of the relationship between PTT and initial IOP. A P value < 0.05 was considered to be statistically significant.

Results

Demographics and Clinical Characteristics of Participants

The present study included 41 POAG patients with unilateral VF loss and 41 age-matched healthy subjects. Among the three groups (VF-affected glaucomatous eyes [A], perimetrically unaffected fellow eyes [B], healthy control eyes [C]), there were no differences in age, sex, central corneal thickness, refraction, axial length, initial IOP, optic disc size, or optic disc cup volume (all $P > 0.05$). The mean IOP during follow-up was 12.6 ± 2.2 mm Hg in group A, 13.5 ± 2.0 mm Hg in group B, and 13.9 ± 3.1 mm Hg in group C, significantly lower in group A than in group B ($P = 0.001$) or group C ($P = 0.041$). The average and vertical cup-to-disc ratios of the optic disc also were significantly higher in group A (0.73 ± 0.07 and 0.74 ± 0.08) than in group B (0.68 ± 0.08 and 0.65 ± 0.09) or group C (0.67 ± 0.09 and 0.63 ± 0.09, $P < 0.001$). The mean deviation of VF was significantly lower in group A (−4.66 ± 6.02 dB) than in group B (−1.20 ± 2.86 dB, $P < 0.001$) or group C (−1.30 ± 2.76 dB, $P = 0.006$). The characteristics of study population are summarized in Table 1.

The retinal nerve fiber layer thickness was significantly thinner in group A than in group B or group C globally and at all quadrants ($P < 0.01$) except the nasal aspect ($P = 0.367$, $P = 0.242$, respectively). There were no significant differences between group B and group C globally or in any of the quadrants ($P > 0.05$). All comparisons among the three groups of the RNFL thicknesses in the four quadrants, and their averages, are provided in Table 2.

Measurement Reproducibility of LC Parameters

In all eyes, the prelaminar tissue and anterior laminar surface were visualized; there was no image excluded due to inability to define the prelamina and anterior border of the LC. Anterior prelaminar depth measurement by the two raters showed excellent intrarater (ICC = 0.992, 95% CI = 0.984–0.996 for rater 1; ICC = 0.998, 95% CI = 0.993–0.999 for rater 2) and interrater (ICC = 0.984, 95% CI = 0.967–0.993) reproducibility (all $P < 0.001$). Lamina cribrosa depth measurement by the two raters, likewise, exhibited excellent intrarater (ICC = 0.979, 95% CI = 0.955–0.990 for rater 1; ICC = 0.984, 95% CI = 0.965–0.992 for rater 2) and interrater (ICC = 0.981, 95% CI = 0.959–0.991) reproducibility (all $P < 0.001$). Prelaminar tissue thickness measurement by the two raters similarly showed excellent intrarater (ICC = 0.964, 95% CI = 0.924–0.983 for rater 1; ICC = 0.968, 95% CI = 0.932–0.985 for rater 2) and interrater (ICC = 0.975, 95% CI = 0.947–0.988) reproducibility (all $P < 0.001$).

Table 2. Comparison of RNFL Thickness Among Glaucomatous Eyes With VF Loss (Group A), Perimetrically Unaffected Fellow Eyes (Group B), and Healthy Control Eyes (Group C)

				*A–B**		*A–C*†		*B-C*†	
Location	**Group A**	**Group B**	**Group C**	***t*-Test**	***P* Value**	***t*-Test**	***P* Value**	***t*-Test**	***P* Value**
Superior, μm	97.12 ± 2.84	112.32 ± 2.34	113.23 ± 2.19	−5.573	<0.001	−4.453	<0.001	−0.284	0.777
Temporal, μm	62.78 ± 1.69	68.39 ± 1.67	69.19 ± 1.59	−3.573	0.001	−2.752	0.007	−0.347	0.730
Inferior, μm	85.07 ± 3.19	110.61 ± 2.44	113.56 ± 2.87	−10.601	<0.001	−6.619	<0.001	−0.787	0.434
Nasal, μm	64.78 ± 1.66	63.34 ± 1.22	67.29 ± 1.32	0.913	0.367	−1.179	0.242	−1.202	0.061
Global, μm	78.17 ± 1.58	88.95 ± 1.28	90.56 ± 1.41	−7.787	<0.001	−5.835	<0.001	−0.847	0.400

* Paired *t*-test.
† Independent *t*-test.

Interindividual and Intraindividual Comparisons of LC Parameters

The anterior prelaminar depth and LCD were significantly greater in group A (460.88 ± 139.05 and 584.46 ± 127.41 μm) than in the other groups (group B, 384.35 ± 131.67 μm and 536.70 ± 126.90 μm, $P < 0.001$; group C, 296.00 ± 154.98 μm and 505.22 ± 130.01 μm, $P < 0.001$). The anterior prelaminar depth in group B was significantly greater than in group C ($P = 0.020$, $P = 0.003$, respectively); however, no significant change of LCD was found between group B and group C ($P = 0.356$).

Prelaminar tissue was significantly thinner in group A (121.99 ± 50.75 μm) than in the other groups (group B, 146.34 ± 40.28 μm, $P = 0.007$; group C, 209.23 ± 116.74 μm, $P < 0.001$). Also, it was significantly thinner in group B than in group C ($P = 0.003$; Fig. 2; Table 3).

Factors Associated With PTT

Linear regression analysis was performed separately to avoid interaction between both eyes. In univariate analysis model 1 (including VF-affected glaucomatous eyes and healthy control eyes), the factors associated with PTT were initial IOP ($P = 0.026$), average and vertical cup-to-disc ratio ($P < 0.001$), optic disc rim area ($P = 0.001$), and mean RNFL thickness ($P = 0.004$). Among these variables, according to multivariate analysis model 1, initial IOP ($\beta = -3.851$, $P = 0.032$) was significantly associated with PTT (Table 4). In univariate analysis model 2 (including perimetrically unaffected fellow eyes and healthy control eyes), the factors associated with PTT were initial IOP ($P = 0.022$), average cup-to-disc ratio ($P = 0.001$), vertical cup-to-disc ratio ($P < 0.001$), optic disc rim area ($P = 0.033$), optic disc cup volume ($P = 0.016$), and mean RNFL thickness ($P = 0.019$). Among these variables, according to multivariate analysis model 2, initial IOP ($\beta = -5.970$, $P = 0.041$) was significantly associated with PTT (Table 5).

A Pearson correlation analysis was performed to evaluate the relationship between the initial IOP and PTT in each of the three groups. In both group A and group B, PTT showed a negative correlation with initial IOP ($r = -0.344$, $P = 0.034$ and $r = -0.410$, $P = 0.008$, respectively), but did not show any significant correlation with initial IOP in group C ($r = -0.067$, $P = 0.677$; Fig. 3). However, no definite association between age and any of the anterior LC parameters (APLD, LCD, or PTT) was found in a total of 123 eyes when partial correlation analysis was applied to correct for mean deviation (MD). Even in the subgroup analysis of glaucoma stage and MD values, no significant age/LC parameter correlation was shown (Supplementary Table S1).

Representative Cases

Representative images of POAG patients with unilateral VF loss and healthy control eyes are shown in Figure 4. In these cases, the PTT differed among the eyes: the prelaminar tissue of the healthy control eye was the thickest (262 μm), followed by the VF-unaffected fellow eye (153 μm); the prelaminar tissue of the VF-affected glaucomatous eye, meanwhile, was the thinnest (106 μm). Similar trends were found for the other LC parameters. For example, the APLD values for the VF-affected glaucomatous eye, perimetrically unaffected fellow eyes, and healthy control eye were 535, 473, and 174 μm, respectively.

Discussion

The main purpose of the present study was to investigate, by SS-OCT, the LC parameters in glaucoma patients with unilateral VF loss and healthy subjects. The anterior prelaminar depth was significantly deeper and the PTT was significantly thinner in the perimetrically unaffected fellow eyes than in the healthy control eyes. The prelaminar tissue thickness was significantly associated with initial IOP in the overall study population.

Structural changes in VF-unaffected eyes of glaucoma patients have been largely investigated.[19–22] In this study, we observed changes of APLD and PTT in the absence of RNFL defect in the fellow eyes of unilateral glaucoma subjects. Xu et

Table 3. Comparison of LC Parameters Among Glaucomatous Eyes With VF Loss (Group A), Perimetrically Unaffected Fellow Eyes (Group B), and Healthy Control Eyes (Group C)

				*A–B**		*A–C*†		*B–C*†	
Location	**Group A**	**Group B**	**Group C**	***t*-Test**	***P* Value**	***t*-Test**	***P* Value**	***t*-Test**	***P* Value**
APLD, μm	460.88 ± 21.71	384.35 ± 20.56	296.00 ± 33.04	5.043	<0.001	4.310	<0.001	2.386	0.020
LCD, μm	584.46 ± 19.90	536.70 ± 19.82	505.22 ± 27.71	4.059	<0.001	2.950	<0.001	0.931	0.356
PTT, μm	121.99 ± 7.93	146.34 ± 6.29	209.23 ± 24.89	−2.819	0.007	−4.133	<0.001	−3.137	0.003
BMO, μm	1758.28 ± 33.79	1737.05 ± 31.15	1784.25 ± 38.25	0.880	0.086	−0.481	0.632	−0.926	0.358

* Paired *t*-test.
† Independent *t*-test.

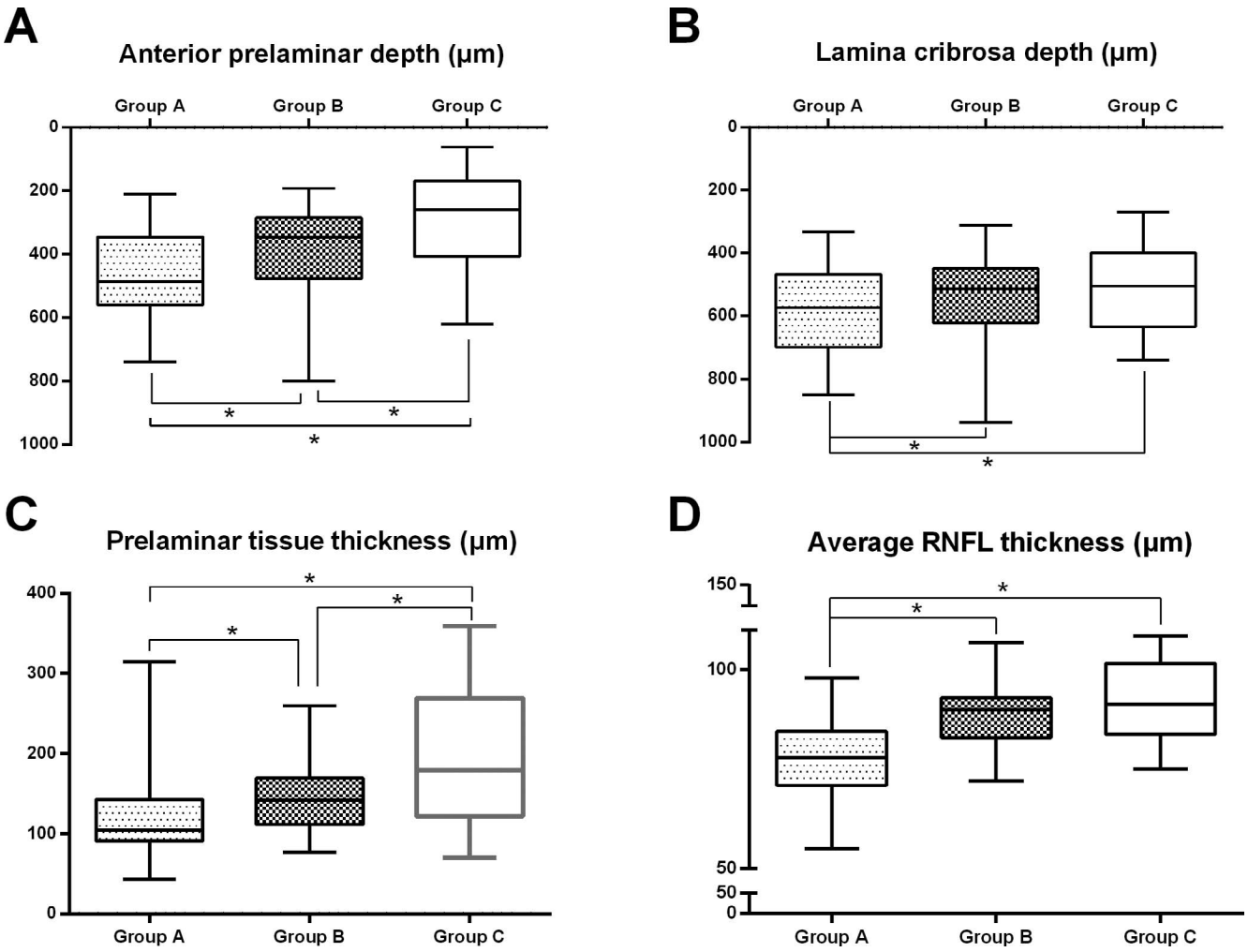

FIGURE 2. The anterior prelaminar depth (**A**), LCD (**B**), PTT (**C**), and average RNFL thickness (**D**) in glaucoma patients with unilateral VF loss and normal controls.

al.[23] also reported that ONH surface depression manifested prior to RNFL defect. And consistently, in previous animal experiments, LC posterior deformation appeared prior to RNFL change in response to IOP elevation.[24,25] A wide spectrum of ONH change can be present in perimetrically unaffected fellow eyes, though the temporal relationship has not yet been fully elucidated.

The optic nerve head, in the pathophysiology of glaucoma, has been considered to be affected by IOP-related stress and strain.[3,26,27] Several research groups have suggested that increased IOP, even within the normal range induces structural deformation of the load-bearing connective tissues and causes posterior displacement of the LC, which then initiates the early stages of glaucoma in susceptible patients. In glaucoma, there are both irreversible and reversible components of posterior LC displacement. Early-glaucomatous monkey eyes, for example, have shown two kinds of deformations of the LC experimentally: plastic (irreversible) and elastic (reversible).[1,25] Previous histologic and in vivo studies have shown that the LC is located more posteriorly within the ONH in

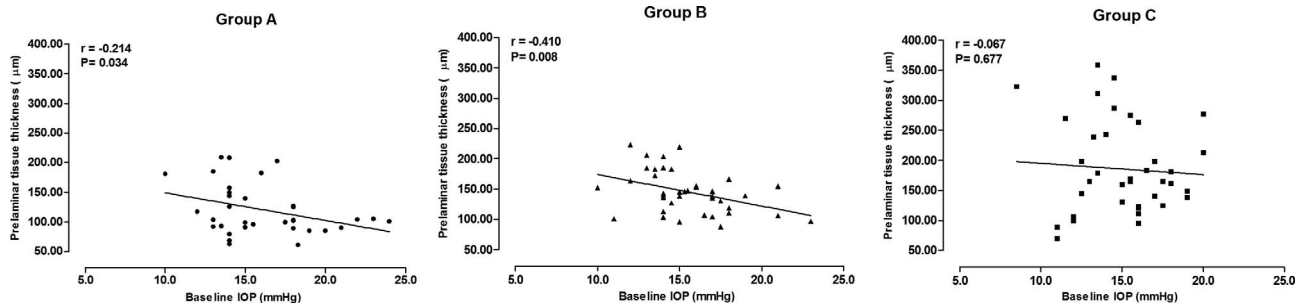

FIGURE 3. Scatterplot showing PTT against baseline IOP in glaucomatous eyes with VF loss (group A, *left*), perimetrically unaffected fellow eyes (group B, *middle*), and healthy control subjects (group C, *right*).

Table 4. Factors Associated With PTT Including VF-Affected Glaucomatous Eyes and Healthy Control Eyes (Model 1)

		Univariate Analysis		Multivariate Analysis*	
Variable	**Unit**	**β**	***P* Value**	**β**	***P* Value**
Age	1 y	−0.027	0.832		
Sex, male		0.185	0.147		
Central corneal thickness	1 μm	0.214	0.144		
Spherical equivalent		0.244	0.139		
Axial length	1 mm	0.095	0.618		
Initial IOP	1 mm Hg	**−0.280**	**0.026**	**−0.219**	**0.032**
IOP during follow-up	1 mm Hg	−0.038	0.769		
Average cup-to-disc ratio		−0.458	**<0.001**	0.173	0.526
Vertical cup-to-disc ratio		−0.535	**<0.001**	−0.611	0.076
Optic disc rim area	1 mm^2	0.411	**0.001**	0.042	0.809
Optic disc size	1 mm^2	−0.037	0.773		
Optic disc cup volume	1 mm^3	−0.238	0.062		
Mean RNFL thickness	1 μm	0.364	**0.004**	0.058	0.705
MD	1 dB	0.200	0.160		
BMO	1 μm	−0.174	0.173		

Statistical analysis was performed using the general linear model. Statistically significant values are shown in bold.

* Factors with $P < 0.05$ in the univariate analysis were included from the multivariate analysis.

Table 5. Factors Associated With PTT Including Perimetrically Unaffected Fellow Eyes and Healthy Control Eyes (Model 2)

		Univariate Analysis		Multivariate Analysis*	
Variable	**Unit**	**β**	***P* Value**	**β**	***P* Value**
Age	1 y	0.081	0.530		
Sex, male		0.139	0.276		
Central corneal thickness	1 μm	0.192	0.192		
Spherical equivalent		0.275	0.094		
Axial length	1 mm	0.109	0.568		
Initial IOP	1 mm Hg	**−0.301**	**0.022**	**−0.217**	**0.041**
IOP during follow-up	1 mm Hg	−0.156	0.223		
Average cup-to-disc ratio		−0.421	**0.001**	−0.166	0.605
Vertical cup-to-disc ratio		−0.470	**<0.001**	−0.477	0.085
Optic disc rim area	1 mm^2	0.271	**0.033**	0.129	0.341
Optic disc size	1 mm^2	−0.152	0.238		
Optic disc cup volume	1 mm^3	−0.305	**0.016**	0.050	0.771
Mean RNFL thickness	1 μm	0.298	**0.019**	0.150	0.235
MD	1 dB	−0.248	0.080		
BMO	1 μm	−0.103	0.421		

Statistical analysis was performed using the general linear model. Statistically significant values are shown in bold.

* Factors with $P < 0.05$ in the univariate analysis were included from the multivariate analysis.

glaucomatous eyes than in healthy eyes.[6,28,29] Meanwhile, the reversible component has been identified as reversal of LC displacement after glaucoma surgery.[30,31] Our results showed that the anterior surface of the LC was more deeply located even after significant reduction of IOP, thus indicating that the change is a irreversible component in glaucomatous eyes.

Posterior displacement of the LC has certainly been a popular topic of research.[30,32,33] The results of a previous in vitro study showed that elevated IOP can cause the LC to deflect posteriorly,[34] leading to its curvature change.[9] He et al.[24] observed longitudinal change of ONH in an experimental monkey model, demonstrating that ONH surface change precedes the changes of RNFL, scanning laser perimetry, and multifocal electroretinography. In addition, Agoumiet al.[35] visualized a significant prelaminar tissue displacement with no significant posterior LC displacement after acute IOP elevation by SD-OCT. The present study showed that in the preperimetric stage, the APLD increased but that the RNFL thickness did not show any differences. Our findings suggest that this change was independent of changes in the axonal components. Longitudinal prospective studies are needed to define serial ONH changes.

Associations between IOP and LC parameters have been demonstrated in several studies. Acute IOP elevation was positively associated with prelaminar tissue displacement but not with laminar displacement in an experimental in vivo study of glaucoma patients and healthy controls. Jung et al.,[36] after demonstrating a positive correlation between initial IOP and LCD ($r = 0391$, $P < 0.001$) in glaucoma patients, suggested that initial IOP is the most decisive factor for LC displacement. Zhao et al.,[37] in an animal study using cats, showed that as IOP increased, the thicknesses of both the LC and prelaminar tissue decreased and, further, that the thickness variation of the LC correlated significantly with the IOP increase when the IOP was higher than 60 mm Hg. Our present univariate and multivariate analyses demonstrated a negative correlation between PTT and the initial IOP in both VF-affected glaucomatous eyes and perimetrically unaffected fellow eyes. This finding suggests that IOP-related stress, even within the normal range of IOP, can affect the prelaminar tissue in the very early stage of glaucoma, though the precise mechanism of IOP-related glaucomatous optic nerve damage remains to be elucidated.

Several studies have shown that age is one of the important factors related to anterior LC displacement in glaucoma patients. Jung et al.[36] showed a negative correlation between age and anterior LCD, and Ren et al.[38] demonstrated that age-related difference increased with advancing disease severity. In the present study, however, no definite association between age and any of the anterior LC parameters (APLD, LCD, or PTT) was found in a total of 123 eyes when partial correlation analysis was applied to correct for MD. Even in the subgroup analysis of glaucoma stage and MD values, no significant age/LC parameter correlation was shown (Supplementary Table S1). Previous studies on the association between age and LC parameters have included large numbers of patients with high tension glaucoma or ocular hypertension.[36,38] By contrast, Rho et al.[39] found no significant correlation between age and LCD in a group of normal tension glaucoma patients. The majority (36 of 41) of the glaucoma patients in the present study, moreover, were POAG patients with untreated IOP $\leq$ 21 mm Hg. These findings suggest that age-related differences in LC displacement would not be shown in glaucoma patients with IOP within the normal range.

Myopic eyes might show larger and more elongated optic discs than do emmetropic eyes. This optic disc enlargement can be explained, in part, by stretching of the disc and deformation of the LC. In our current study, there were some

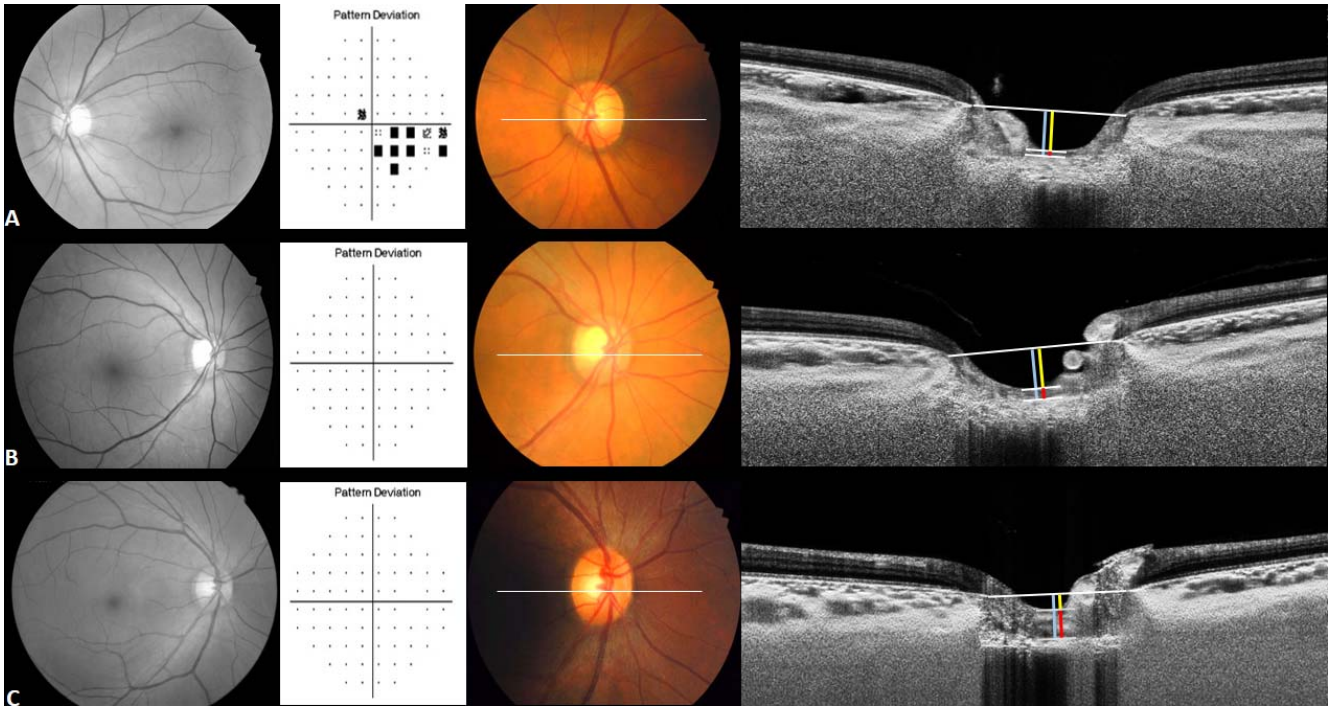

FIGURE 4. Representative cases: Red-free RNFL photo, VF examination, optic disc and SS-OCT B-scans. In the SS-OCT B-scans, the reference line (*white horizontal line*) connecting the end of the Bruch's membrane and three vertical colored-lines from the reference line are marked. The anterior prelaminar depth (APLD), LCD, and the PTT are marked by *yellow*, *blue*, *red lines*. (**A**) A 62-year-old glaucoma patient with unilateral VF loss (intraocular pressure of 12–19 mm Hg on medication) had superior temporal RNFL loss in RNFL photo and mild VF defect at inferonasal side; the MD on standard automated perimetry was −2.9 decibels (dB); The anterior prelaminar depth, LCD, and PTT were 535, 641, and 106 μm, respectively. (**B**) A fellow eye shown in panel **B** (intraocular pressure of 14–15 mm Hg without medication) had normal VF; the MD was 0.80 dB. The anterior prelaminar depth, LCD, and PTT were 473, 606, and 153 μm, respectively. (**C**) A 35-year-old man is normal control subject. The anterior prelaminar depth, LCD, and PTT were 174, 436, and 262 μm, respectively.

differences in optic disc size and axial length among the groups, though they were not statistically significant. One may argue that the degree of myopia can affect ONH deformation, such as by tilting or cyclotorsion, which could have biased the results. However, several studies have shown that in the range of −5 to +5 diopters of refractive error, there is no association with optic disc size.[40–42] In the present study, the spherical refractions of the subjects mostly ranged from −5.0 to +3.0 diopters. Given that we intentionally excluded the highly myopic patients, the myopic effect can be considered to have been minimized and, therefore, not significantly influential to our results in terms of bias.

Study Limitations

This study has several limitations. First, only the central three points in each B-scan were measured in this study. The posteriorly bowed nature of the LC, however, can be seen more prominently in the central region; the best representation of LC-structural characteristics, therefore, might be obtained by measurement of the central area of the ONH. Moreover, precise measurement of LCD was not the present study's purpose; the goal, rather, was to compare the LC parameters and to determine any correlation between glaucomatous damage and posterior displacement of the LC. The same methodology was applied to all of the study participants in order to eliminate any significant bias from the study.

Second, the majority of the glaucoma patients (36 out of 41 patients) in the present study were POAG patients with untreated IOP $\leq$ 21 mm Hg. Therefore, our conclusions should not be generalized to high-IOP glaucoma patients. Further investigation should focus on the comparative characteristics of the fellow eyes of normal-IOP and high-IOP glaucoma patients.

Third, in the analysis of the APLD and LCD measurements, the tilt of the disc surface was not adjusted for, which may lead the analysis in a nonstandardized fashion throughout the lamina. In accordance with the correlation between myopia and optic disc tilt, however, the spherical refractions of the subjects ranged from −8.0 to +3.0 diopters, and only four subjects had spherical refraction over −5.0 diopters. Therefore, adjustment for the optic disc tilt probably would not have affected the results in any case.

Finally, due to the cross-sectional nature of the present study, the causal relationship between prelaminar change and LC displacement remains unclear. Longitudinal study might be needed for clarification.

In summary, APLD was significantly greater and prelaminar tissue was significantly thinner in the fellow eyes of glaucoma patients with unilateral VF loss than in healthy control eyes. These findings suggest that subclinical or preperimetric changes of the LC and/or prelaminar tissue are already present in the fellow eyes of individuals with unilateral glaucoma. Optical coherence tomography may have the potential to detect subclinical LC changes in the early stage of glaucoma.

Acknowledgments

Supported by grants of the Korea Health technology R&D Project, Ministry of Health & Welfare, Republic of Korea (Grant Number: HI12C1499) and NUS Young Investigator Award (NUSYIA_FY13_P03, R-397-000-174-133). The funding organization had no

role in the design or conduct of this research. The authors alone are responsible for the content and writing of the paper.

Disclosure: **D.W. Kim**, None; **J.W. Jeoung**, None; **Y.W. Kim**, None; **M.J.A. Girard**, None; **J.M. Mari**, None; **Y.K. Kim**, None; **K.H. Park**, None; **D.M. Kim**, None

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