Posterior Displacement of the Lamina Cribrosa in Glaucoma: In Vivo Interindividual and Intereye Comparisons

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Purpose. We assessed in vivo lamina cribrosa (LC) position within the optic nerve head in glaucoma.

Methods. For interindividual comparison, glaucoma patients at various stages and normal subjects were recruited. For intraindividual, intereye comparison, glaucoma patients with visual field (VF) defects in only one eye were recruited separately. Serial horizontal and vertical enhanced depth imaging optical coherence tomography (EDI OCT) B-scans of the optic nerve head were obtained prospectively from each participant. Mean and maximum anterior LC depths were measured in 11 equally spaced horizontal B-scans, excluding the LC insertion area under the Bruch's membrane and scleral rim.

Results. Totals of 47 glaucomatous eyes (47 patients; VF mean deviation, −12.7 ± 8.2 dB) and 57 normal eyes (57 subjects) were enrolled for the interindividual comparison. Mean and maximum LC depths were significantly greater in the glaucomatous than in the normal eyes in all 11 scans (all $P < 0.03$). There were 54 glaucoma patients with VF defects in only one eye (VF mean deviation, −15.6 ± 8.8 dB) included in the intereye comparison. Mean and maximum LC depths were significantly greater in the eyes with VF defects than in the fellow eyes with no VF defects in all 11 scans (all $P < 0.01$).

Conclusions. The central and midperipheral LC is located more posteriorly in glaucomatous than in normal eyes, as well as in eyes with VF defects compared to fellow eyes with no VF defects. These results support the concept of posterior LC displacement in glaucoma and provide the basis for future in vivo human studies.

Keywords: lamina cribrosa, glaucoma posterior segment, optical coherence tomography

The lamina cribrosa (LC) is a mesh-like structure within the scleral canal of the optic nerve head traversed by axons of retinal ganglion cells.[1–3] There is increasing evidence that structural changes in the LC are implicated in the pathophysiology of glaucomatous optic neuropathy.[3–9]

LC anatomy within the optic nerve head (LC displacement) has been investigated in different conditions.[7–19] Histologic studies of monkey eyes with experimental glaucoma demonstrated backward displacement of the LC.[9–13] Posterior LC displacement also was described in histologic studies using normal human donor eyes with artificially elevated IOP after enucleation[14] and using glaucomatous eyes.[7,8] Other investigators reinforced the idea of posterior LC displacement in glaucoma using computerized modeling.[17–19]

However, posterior LC displacement in glaucoma has not been demonstrated in living human eyes to our knowledge. Various ocular imaging devices have been used to investigate the LC in vivo.[15,20–29] Among such technologies, enhanced depth imaging optical coherence tomography (EDI OCT)[30] improves the visualization of the deep optic nerve head structures, including the LC, and allows a more reliable identification of the LC position.[28,29,31]

The purpose of our study was to compare the LC position using EDI OCT between glaucoma patients and normal subjects (interindividual comparison), and between the two eyes of glaucoma patients with unilateral visual field (VF) loss (intraindividual, intereye comparison) to ascertain whether the LC is displaced posteriorly in association with glaucomatous damage.

Methods

This was a cross-sectional analysis of data obtained from an ongoing, prospective, longitudinal study approved by the New York Eye and Ear Infirmary, and the State University of New York at Buffalo institutional review boards. Written informed

consent was obtained from all subjects, and the study adhered to the tenets of the Declaration of Helsinki.

For interindividual comparison of the LC position, we recruited prospectively open-angle glaucoma patients with a range of optic disc and VF abnormalities representing various stages of glaucomatous damage from the authors' glaucoma referral practice. We also recruited healthy volunteers from office workers, and their friends and family members. Glaucoma was defined by the presence of characteristic optic disc damage (localized or diffuse neuroretinal rim thinning or retinal nerve fiber layer defect) associated with typical, reproducible VF defects (glaucoma hemifield test result outside normal limits and/or the presence of at least 3 contiguous test points within the same hemifield on the pattern deviation plot at $P < 1\%$, with at least 1 point at $P < 0.5\%$ on at least 2 consecutive VF tests, with reliability indices better than 15%). Normal subjects were required to have normal-appearing open iridocorneal angles, IOP between 10 and 21 mm Hg, clinically normal optic discs and VFs, and no apparent ocular or systemic abnormalities that could affect the optic nerve structure or visual function.

For intraindividual, intereye comparison of the LC position, we recruited separately open-angle glaucoma patients with VF defects in only one eye, irrespective of the presence or absence of possible glaucomatous disc changes in the eye with no VF defects.

All participants underwent slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, and stereoscopic optic disc examination. For both eyes of each participant, serial horizontal and vertical B-scan images (interval between images, approximately 30 μm) of the optic nerve head were obtained using EDI OCT (Spectralis; Heidelberg Engineering, GmbH, Dossenheim, Germany). Patients with glaucoma underwent simultaneous color disc stereophotography (Stereo Camera Model 3-DX; Nidek, Inc., Palo Alto, CA) and standard automated perimetry (Humphrey Visual Field Analyzer, 24-2 Swedish interactive threshold algorithm standard strategy; Carl Zeiss Meditec, Inc., Dublin, CA) within 3 months of EDI OCT imaging. Age and IOP on the date of EDI OCT, self-reported ethnicity, VF mean deviation (MD) within 3 months from the date of EDI OCT, and glaucoma diagnosis were recorded. We excluded eyes with previous posterior segment intraocular surgery or ocular trauma, systemic or ocular conditions other than glaucoma known to affect the optic nerve structure or VF, and EDI OCT images of poor quality with focally or diffusely unclear images (e.g., very small optic disc, prominent vascular shadow, media opacity, poor patient cooperation), or significant artifacts (e.g., mirror artifacts, out-of-range artifacts, z-alignment failure). We also excluded eyes with torted optic discs (the axis of longest disc diameter differed by $>10^\circ$ from the vertical axis of the disc) because the LC structure in those eyes may be different from that in nontorted discs. This is a stricter definition than that used in the Blue Mountains Eye Study.[32]

For EDI OCT of the optic nerve head, we used the method described in our previous reports.[25,31] In brief, the OCT device was set to image a $15^\circ \times 10^\circ$ rectangle for horizontal scans (and a $10^\circ \times 15^\circ$ rectangle for vertical scans) centered on the optic disc. This rectangle was scanned with 97 sections; each section had 20 OCT frames averaged. The device was moved closer to the eye to place the zero reference plane more posteriorly, which enhanced the image quality of deeper optic nerve head structures. This created an inverted image with the inner portions of the retina shown facing downward. The OCT images shown in this publication were inverted after being exported from the OCT device and are negative images, with Bruch's membrane appearing black rather than white and with vascular shadows appearing as white vertical streaks.

To measure the LC depth, we used and modified the method described in our previous report.[25] For one randomly selected eye of each participant, mean and maximum LC depths were measured in 11 horizontal B-scans that were spaced equally along the vertical diameter of the LC (Fig. 1C). The distance between adjacent scans among the 11 scans was adjusted based on the vertical diameter of the LC (greater interval between scans for a larger LC). The line connecting Bruch's membrane edges was used as a reference plane for all depth measurements.[15,25,26,28,33,34] A line perpendicular to this reference line was drawn from each Bruch's membrane edge to the anterior surface of the LC (Fig. 1A). When one of these two perpendicular lines did not meet the anterior laminar surface because of disc tilting and associated lateral LC displacement, a line was drawn from the anterior LC insertion point perpendicularly to the line connecting the two Bruch's membrane edges (Fig. 1B). The area surrounded by these two perpendicular lines, the line connecting Bruch's membrane edges, and the anterior laminar surface was measured (Figs. 1A, 1B, area S). The mean LC depth at each of the 11 horizontal EDI OCT scans was defined by area S divided by length D (Figs. 1A, 1B). All measurements were performed using ImageJ software (developed by Wayne Rasband, National Institutes of Health, Bethesda, MD; available in the public domain at http://rsb.info.nih.gov/ij/index.html). The anterior laminar surface was delineated manually as if the LC had no pores, including those for retinal vessels. When the target microstructures were not visualized clearly, an adjacent horizontal EDI OCT scan, approximately 30 μm apart from the original scan, was used for measurement. When the target microstructures were not visualized clearly even in the adjacent scans, we excluded that eye. All measurements were performed by an experienced observer, who was masked to the clinical information of subjects, including the infrared optic disc images provided by the OCT device.

To evaluate the intraobserver and interobserver reproducibility of LC depth measurement, 20 randomly selected EDI OCT B-scans from 20 normal eyes were evaluated. Analysis was based on 3 independent series of re-evaluations made by 2 independent observers. The absolute agreement of a single observer's measurement and the mean of all 3 measurements conducted by the 2 observers were calculated with the intraclass correlation coefficient (ICC) from a 2-way mixed effect model.

The mean and maximum LC depths in each of the 11 EDI OCT scans were compared between the glaucoma patients and the normal subjects (interindividual comparison), and between the two eyes of glaucoma patients with unilateral VF defects (intereye comparison). The mean LC depth of each eye (the average value of the mean LC depths in 11 scans) and the maximum LC depth of each eye (the maximum value among the maximum LC depths in 11 scans) were calculated and averaged within each group. These values were compared between the glaucoma patients and the normal subjects, and between the two eyes of glaucoma patients with unilateral VF defects. When the LC depths were compared between the glaucoma patients and the normal subjects, P values were calculated before and after controlling for age, IOP, vertical disc diameter, and disc ovality index (vertical disc diameter/horizontal disc diameter), which are potential confounding factors. The horizontal and vertical disc diameters in each eye were measured in the infrared disc photograph provided by the OCT device by another independent observer.

Mean age, IOP, vertical disc diameter, disc ovality index, and LC depths were compared between the glaucoma patients and the normal subjects using independent t-tests because all these parameters followed a normal distribution according to the Shapiro-Wilk test of normality (all $P > 0.05$). When the LC

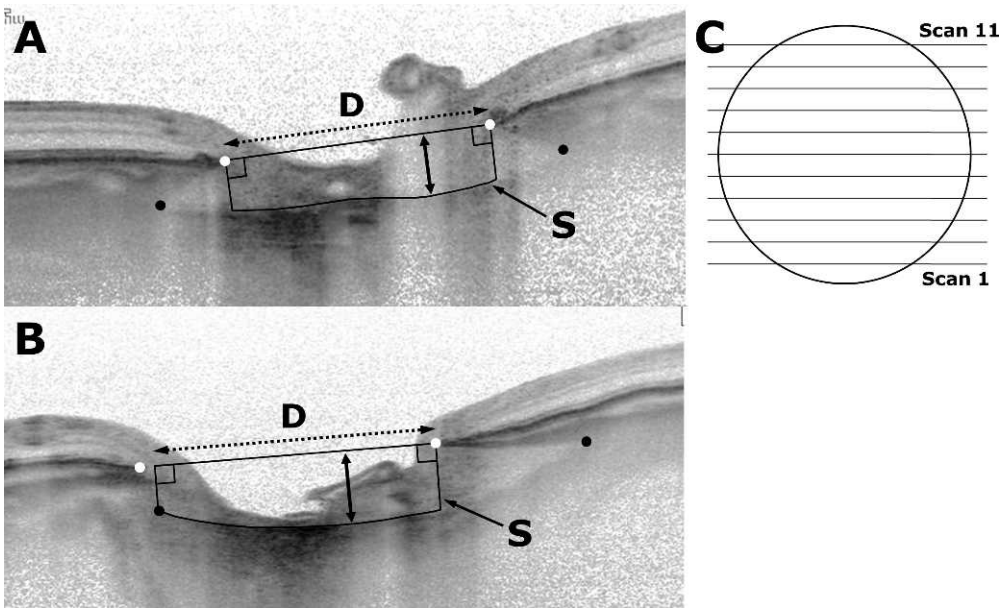

FIGURE 1. (**A**, **B**) After delineating the anterior surface of the LC, the maximum LC depth was measured (*black double arrows*) perpendicularly to the line connecting the two Bruch's membrane edges, and the mean LC depth was approximated by dividing *area S* by *length D* for the LC area under the Bruch's membrane opening, in EDI OCT B-scans obtained (**C**) in 11 equally spaced horizontal scans (scan 1 → 11 = inferior → superior). The *white* and *black dots* in (**A**) and (**B**) indicate Bruch's membrane edges and anterior laminar insertion points, respectively. The *circle* in (**C**) indicates the LC.

depths were compared between the glaucoma patients and the normal subjects controlling for age, IOP, vertical disc diameter, and disc ovality index, analysis of covariance was used. Mean IOP was compared between the two eyes of glaucoma patients with unilateral VF defects using a paired *t*-test because IOP followed a normal distribution according to the Shapiro-Wilk test of normality (all $P > 0.05$). Mean and maximum LC depths were compared between the two eyes of glaucoma patients with unilateral VF defects using Wilcoxon's signed rank test, because none of these parameters followed a normal distribution according to the Shapiro-Wilk test of normality (all $P \leq 0.001$). All statistical analyses were performed using SPSS, version 17.0 (SPSS Inc., Chicago, IL), and statistical significance was defined at $P < 0.05$.

RESULTS

Mean LC depth measurement by the two observers showed excellent intraobserver (ICC = 0.974 and 95% confidence interval [CI] = 0.945–0.989 for observer 1; ICC = 0.961 and 95% CI = 0.920–0.983 for observer 2) and interobserver (ICC = 0.989 and 95% CI = 0.973–0.996) reproducibility (all $P <$ 0.001). Maximum LC depth measurement by the two observers also showed excellent intraobserver (ICC = 0.978 and 95% CI = 0.954–0.991 for observer 1; ICC = 0.959 and 95% CI = 0.916–0.982 for observer 2) and interobserver (ICC = 0.998 and 95% CI = 0.997–0.999) reproducibility (all $P < 0.001$).

Interindividual Comparison

Totals of 47 glaucomatous eyes (47 patients; 21 women) and 57 normal eyes (57 subjects; 27 women) were included for analysis. Mean age, IOP, vertical disc diameter, and disc ovality index were 56 ± 16 (range, 27–85) years, 13.9 ± 2.9 (range, 8–20) mm Hg, 1620 ± 205 (range, 1182–2129) μm, and 1.12 ± 0.11 (range, 0.94–1.41) in the glaucoma group, and 56 ± 17 (range, 22–84) years, 14.7 ± 2.1 (range, 10–19) mm Hg, 1519 ± 187 (range, 1130–1958) μm, and 1.07 ± 0.10 (range, 0.87–1.33) in the normal group. Age and IOP were similar between the two groups ($P = 0.91$ and 0.09, respectively). Vertical disc diameter was significantly larger, and disc ovality index was significantly greater (more tilted disc) in the glaucoma than in the normal group (all $P = 0.01$). Of the subjects, 34 were white, 5 were Hispanic, and 8 were Asian in the glaucoma group, while 45 subjects were white, 5 were Hispanic, and 7 were Asian in the normal group. Mean VF MD of the 47 glaucomatous eyes was −12.7 ± 8.2 (range, −29.6 to −0.5) dB. There were 33 eyes with primary open-angle glaucoma, 7 with exfoliative glaucoma, and 7 with pigmentary glaucoma.

Mean and maximum LC depths were significantly greater in the glaucoma than in the normal groups in all 11 scans (Fig. 2, all $P < 0.03$). The averaged mean LC depth in the glaucoma group was significantly greater than that in the normal group (438 ± 102 [range, 192–698] vs. 353 ± 70 [range, 237–522] μm, $P < 0.001$). The averaged maximum LC depth in the glaucoma group also was significantly greater than that in the normal group (570 ± 124 [range, 276–909] vs. 453 ± 81 [range, 310–647] μm, $P < 0.001$). There was no change in statistical significance after controlling for age, IOP, vertical disc diameter, or disc ovality index. In both groups, mean and maximum LC depth profiles assumed the shape of a W, demonstrating that the LC is more depressed in the inferior and superior midperiphery compared to its central region (Fig. 2).

After Bonferroni correction was applied, the mean and maximum LC depths were significantly greater in 10 of 11 scans (except in scan 1 for mean and maximum LC depths).

Intraindividual, Intereye Comparison

We included for analysis 54 glaucoma patients with VF defects in only one eye (24 women; mean age, 58 ± 16 [range, 22–88] years). Mean IOP was similar between the eyes with VF defects and the fellow eyes with no VF defects (14.9 ± 3.7 [range, 8–21] vs. 15.3 ± 3.0 [range, 8–20] mm Hg, $P = 0.46$). Of the subjects, 40 were white, 7 were Hispanic, and 7 were Asian.

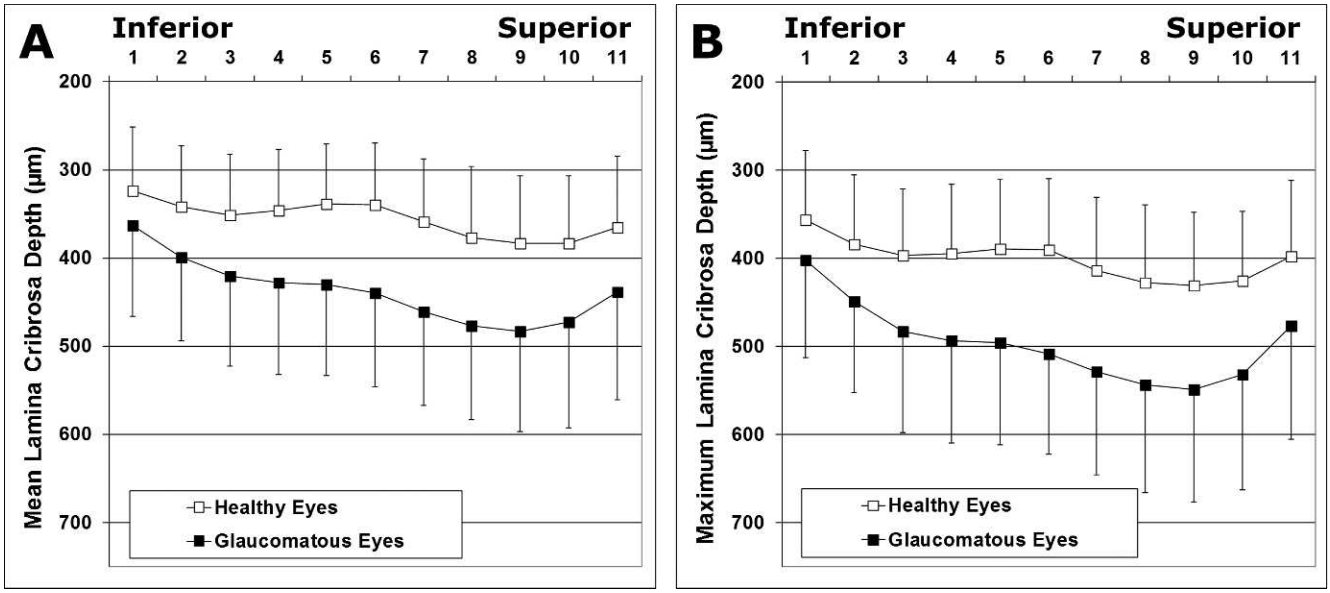

FIGURE 2. (**A**) Mean and (**B**) maximum depth profiles of the anterior LC surface in 11 horizontal EDI OCT scans (scan 1 → 11 = inferior → superior) in the glaucomatous and normal eyes (interindividual comparison). *Error bars* represent SDs. Mean ($P = 0.025$ in scan 1, 0.001 in scan 2, and <0.001 in scans 3–11) and maximum ($P = 0.016$ in scan 1 and <0.001 in scans 2–11) LC depths were significantly greater in the glaucomatous than in the normal eyes.

Mean VF MD of the eyes with VF defects was −15.6 ± 8.8 (range, −32.4 to −0.4) dB. There were 39 eyes with primary open-angle glaucoma, 8 with exfoliative glaucoma, and 7 with pigmentary glaucoma.

Mean and maximum LC depths were significantly greater in the eyes with VF defects than in the fellow eyes with no VF defects in all 11 scans (Fig. 3, all $P < 0.01$). The averaged mean LC depth in the eyes with VF defects was significantly greater than that in the fellow eyes with no VF defects (460 ± 141 [range, 273–1034] vs. 407 ± 94 [range, 247–771] µm, $P < 0.001$). The averaged maximum LC depth in the eyes with VF defects was significantly greater than that in the fellow eyes with no VF defects (585 ± 169 [range, 367–1289] vs. 512 ± 118 [range, 317–993] µm, $P < 0.001$). In both groups, mean and maximum LC depth profiles assumed the shape of a W (Fig. 3), as in the groups in interindividual comparison.

After Bonferroni correction was applied, the mean LC depth was significantly greater in all 11 scans and the maximum LC depth was significantly greater in 10 of 11 scans (except in scan 11).

DISCUSSION

In this in vivo human study, we demonstrated that the LC was located more deeply within the optic nerve head in glaucomatous than in normal eyes, supporting the concept of posterior displacement of the LC in glaucoma described in previous studies using histologic specimens[7–12,14] or computerized modeling.[17–19] Moderate IOP elevation for a relatively short period of time (<1 hour) did not lead to significant posterior displacement of the LC in normal humans or nonhuman primates.[13,15] However, in studies using monkey eyes with early experimental glaucoma and more chronic (>1 month) IOP elevation, the LC was displaced posteriorly compared to its baseline position[16] or the LC in normal fellow eyes.[9] In a study using enucleated or postmortem human eyes, the anterior laminar surface was located more posteriorly relative to the sclera in glaucomatous eyes than in normal ones.[7] In another study using enucleated or postmortem human eyes, the distance from the edge of Bruch's membrane to the posterior laminar surface was similar between glaucomatous and normal eyes, but the LC was significantly thinner in glaucomatous eyes, suggesting posterior displacement of the anterior laminar surface in glaucoma.[8] Studies using numerical modeling suggested that stress and strain related to IOP may be associated with posterior LC displacement in glaucoma, probably as a result of LC connective tissue remodeling.[17–19]

Posterior LC displacement in glaucoma has reversible and irreversible components. Plastic (irreversible) and elastic (reversible) deformations of the LC were shown in monkey eyes with early experimental glaucoma.[9] Irreversible posterior displacement of the LC also was shown in human glaucomatous eyes as posterolateral extension of the anterior laminar surface.[7,8] Reversible component of posterior LC displacement was evidenced by the anterior LC displacement in response to IOP reduction after trabeculectomy.[26,28] Since the IOP was similar between our glaucoma and normal groups (13.9 vs. 14.7 mm Hg, $P = 0.15$), the posterior LC displacement in our glaucoma group in the interindividual comparison likely represented its irreversible component. A more deeply located LC in the glaucoma group also was demonstrated after statistical controlling for IOP.

In intereye comparison in glaucoma patients with unilateral VF loss based on standard automated perimetry, the LC was located more deeply in the eyes with VF defects than in the fellow eyes with no VF defects. High interindividual variability of the optic nerve head size and morphology was demonstrated in a population-based study.[35] In another study, all optic nerve head parameters measured by confocal scanning laser ophthalmoscopy (Heidelberg retina tomograph; Heidelberg Engineering, GmbH) were correlated significantly between the right and left eyes of normal subjects, and there was no significant intereye difference in disc area, cup area, mean and maximum cup depths, and cup-to-disc area ratio.[36] Therefore, the results of our intereye comparison may have been less affected by possible ocular confounding factors (e.g., vertical disc diameter and disc ovality index), as well as by possible systemic confounding factors (e.g., cerebrospinal fluid pressure around the optic nerve), than the results of our

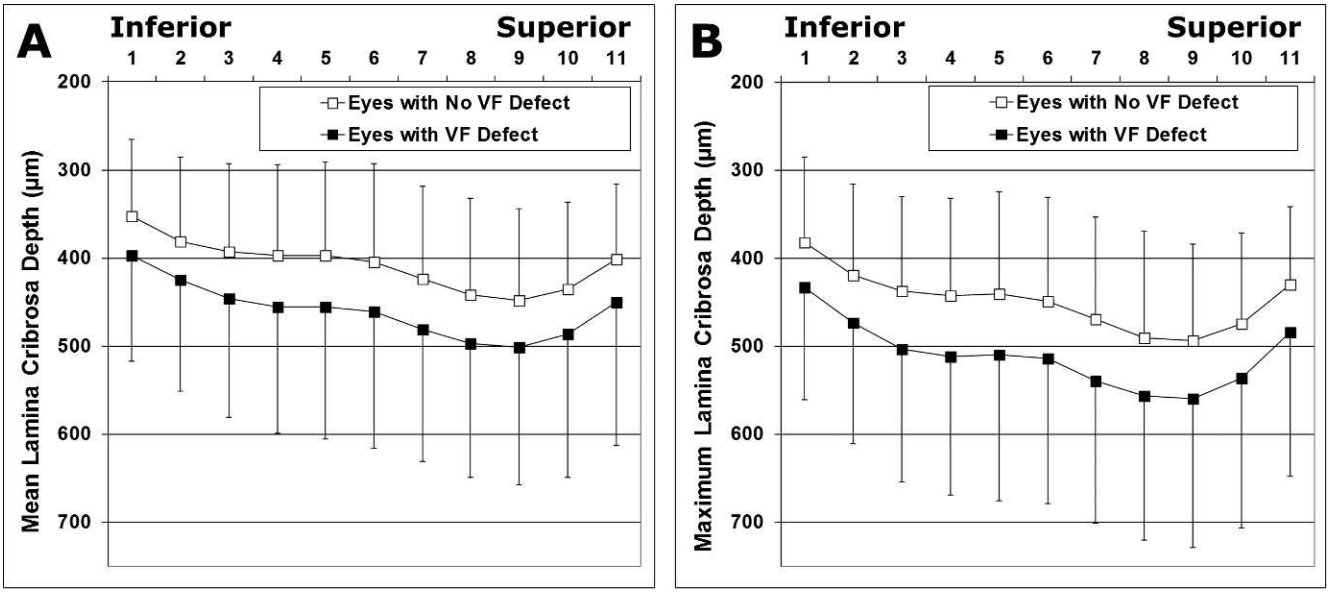

FIGURE 3. (**A**) Mean and (**B**) maximum depth profiles of the anterior LC surface in 11 horizontal EDI OCT scans (scan 1 → 11 = inferior → superior) in the eyes with glaucomatous visual field defects and the fellow eyes with no visual field defects (intraindividual, intereye comparison). *Error bars* represent SDs. Mean ($P = 0.004$ in scan 1, 0.002 in scan 2, <0.001 in scans 3–9, 0.002 in scan 10, and 0.010 in scan 11) and maximum ($P = 0.002$ in scan 1, 0.001 in scan 2, <0.001 in scans 2–10, and 0.004 in scan 11) LC depths were significantly greater in the eyes with visual field defects and the fellow eyes with no visual field defects.

interindividual comparison. Readers should note that the eyes with no VF defect in our glaucoma patients with unilateral VF loss may not have been normal eyes, but may have had glaucomatous disc changes (preperimetric glaucoma). Even if some or all eyes with no VF defect had preperimetric glaucoma, our results of intereye comparison still supported the concept of posterior LC displacement in glaucoma. We believe that our study provided stronger evidence of posterior LC displacement in glaucoma by presenting the results of interindividual and intereye comparisons. Future studies are warranted on the LC depth difference between normal eyes and the eyes with preperimetric glaucoma using a larger sample size.

In our study, we compared the mean and maximum LC depths at 11 levels of the LC from the inferior to the superior areas. The large number of analyses may have increased the chance of a type I error during hypothesis testing. Several methods have been proposed to correct potentially for multiple comparisons in the statistics literature, although there is no consensus on whether they should be applied routinely or what specific method should be employed.[37,38] After Bonferroni correction was applied, the mean and maximum LC depths still were significantly greater in 10 of 11 scans in interindividual and intereye comparisons.

It is important to note that we investigated the LC depth in the LC center and midperiphery (the LC regions under the Bruch's membrane opening), and intentionally excluded the LC far periphery at or near the LC insertion under the Bruch's membrane and scleral rim (Figs. 1A, 1B). In our previous study, we measured the LC depth for the entire LC.[25] In the present study, we may have been able to obtain more objective and reliable data using this newer method, because the LC is visualized less clearly under the Bruch's membrane and the scleral rim than under the Bruch's membrane opening. Mean and maximum LC depth values and profiles in our normal group (Fig. 2) were similar to those reported in our previous study using normal subjects,[25] both demonstrating the horizontal central ridge of the LC. This supported the reliability of both methods for measuring the LC depth.

Focal LC defects were detected in glaucomatous eyes.[27] These defects may have different underlying pathogenic mechanisms from those for posterior LC displacement in glaucoma, and occur mostly in the inferior and superior far periphery of the LC.[27] Because these areas corresponded to the regions inferior to the most inferior scan (scan 1 in Fig. 1C) or superior to the most superior scan (scan 11 in Fig. 1C) in the present study, we could evaluate posterior LC displacement in glaucoma more accurately, not overestimated by focal LC defects, by excluding the inferior and superior far periphery of the LC when measuring the LC depth.

As the error bars in Figures 2 and 3 (standard deviations of the LC depths) showed, there was overlap of LC depths between the normal and glaucomatous eyes, and between the two eyes of glaucoma patients with unilateral VF loss. This finding suggested that there may be subtypes of glaucoma in which the LC does not undergo significant posterior displacement. Therefore, future studies should focus on the difference in the posterior LC displacement between different glaucoma groups (e.g., normal-tension glaucoma versus high-tension glaucoma, European descent versus African descent, emmetropia versus high myopia, different optic disc phenotypes).

Our study is limited by a relatively small sample size. Also, since the averaged mean LC depth in each group was approximated by averaging the mean LC depths in 11 horizontal EDI OCT scans, this value may not represent accurately the true average depth of the entire anterior LC surface in each group. However, the purpose of our study was to compare the LC position between glaucomatous and normal eyes, and ascertain whether the LC is displaced more posteriorly in association with glaucomatous damage, but not to measure the accurate average LC depth in either group. Since we applied the same method to all participants, we believe that our methodology did not cause significantly biased results. The 11 horizontal EDI OCT B-scans may not fall on the exact corresponding parts of the LC in each eye. Therefore, for example, it is inappropriate to compare the LC depth in the scan 4 of one eye to the LC depth in the scan 4 of another eye. However, we compared the "average value" of LC depths at

each of the 11 horizontal scan locations between two groups (Figs. 2, 3), which probably had reduced the bias caused by the fact that the 11 B-scans did not fall on the corresponding parts of the LC in each eye. Additionally, because there was a significant difference between the two groups in all 11 scan locations (Figs. 2, 3), we think that it is appropriate to conclude that the LC depth is significantly different between the groups. In our previous article,[25] we defined the maximum LC depth of an eye as "the average value of the maximum LC depths in 11 EDI OCT B-scans." In the present study, however, we decided to define the maximum LC depth of an eye as "the greatest value among the maximum LC depths in 11 EDI OCT B-scans." We believe that this new definition is more meaningful scientifically and clinically than the definition used in our previous article.[25]

In summary, our results of interindividual and intereye comparisons in living human eyes supported the concept of posterior LC displacement, and provided the basis for future in vivo human studies in glaucoma. An in vivo longitudinal study on the LC position may confirm that the posterior LC displacement is one of structural changes during the glaucomatous process, and elucidate the relationship between the LC deformation and the structural or functional progression of glaucoma.

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