Lamina Cribrosa Depth in Different Stages of Glaucoma

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Purpose. To compare lamina cribrosa (LC) depth between normal eyes and eyes with different stages of treated glaucoma.

Methods. Serial enhanced depth imaging (EDI) optical coherence tomography (OCT) B-scans of the optic nerve head were obtained. To generate the mean LC depth for each eye, LC depths were measured in 11 equally spaced horizontal B-scans and averaged. The mean LC depth was compared among normal, preperimetric, mild-to-moderate, and severe glaucoma groups. Among patients with visual field (VF) loss, correlation analysis was performed (1) between mean LC depth and VF mean deviation (MD), and (2) between mean LC depth and retinal nerve fiber layer (RNFL) thickness.

Results. Eighty-six normal eyes (age, 56 ± 14 years), 47 preperimetric glaucoma eyes (age, 60 ± 16 years), 55 mild-to-moderate glaucoma eyes (age, 59 ± 16 years; VF MD, -6.0 ± 3.2 dB), and 60 severe glaucoma eyes (age, 59 ± 17 years; VF MD, -19.7 ± 6.1 dB) were included. Mean LC depth was significantly greater in preperimetric glaucoma than in normal eyes (390 vs. 344 µm, $P = 0.004$) and in mild-to-moderate than in preperimetric glaucoma eyes (448 vs. 390 µm, $P = 0.001$). However, no significant difference was observed between mild-to-moderate and severe glaucoma eyes (448 vs. 437 µm, $P = 0.52$). No correlation was observed between LC depth and VF MD ($P = 0.56$) or RNFL thickness ($P = 0.90$) in glaucomatous eyes with VF loss.

Conclusions. In treated glaucoma, posterior LC displacement occurs mostly in the preperimetric and mild-to-moderate glaucoma stages. This warrants further investigation of LC depth as a parameter to monitor glaucoma progression in the early stages.

Keywords: lamina cribrosa, glaucoma, visual field

The lamina cribrosa (LC) is a mesh-like structure at the optic nerve head that surrounds and supports the retinal ganglion cell axons as they form the optic nerve.[1–3] Deformation and displacement of the LC have been increasingly implicated as the primary pathophysiologic mechanism of glaucomatous optic neuropathy.[4–6]

Posterior LC displacement has been demonstrated in histologic studies using monkey eyes with experimental glaucoma, ex vivo human eyes with artificially elevated intraocular pressure (IOP), and postmortem glaucomatous eyes.[7–12] Biomechanical computer modeling and in vivo imaging, such as enhanced depth imaging (EDI) optical coherence tomography (OCT), have further elucidated the LC microstructure and improved our ability to detect its position, features, and integrity.[13–21] Posterior LC displacement and focal LC defects as seen on EDI OCT have been linked to glaucomatous optic disc and visual field (VF) changes in human eyes in vivo.[22–26] However, the trajectory of LC displacement as glaucoma severity increases is unknown. Discovering a linear or exponential pattern, whether increasing or decreasing, between LC position within the optic nerve head and disease severity could direct future diagnostics and treatment.

The purpose of our cross-sectional study was to assess the posterior displacement of the LC by comparing the LC position in vivo in normal subjects and glaucoma patients at different stages of disease. This will serve as a starting point for future longitudinal studies to demonstrate a time course for LC displacement as glaucoma advances.

METHODS

This study was approved by the New York Eye and Ear Infirmary Institutional Review Board. Written, informed consent was obtained from all subjects, and the study adhered to the tenets of the Declaration of Helsinki.

As part of an ongoing, prospective, longitudinal study, we recruited normal subjects and glaucoma patients with a range of VF loss representing various degrees of glaucomatous optic neuropathy (primary open-angle glaucoma, exfoliative glaucoma, pigmentary glaucoma, or primary chronic angle-closure glaucoma). Glaucoma was defined by the presence of characteristic optic disc and/or retina changes (localized or diffuse neuroretinal rim thinning or retinal nerve fiber layer [RNFL] defect) on stereo disc photographs, irrespective of
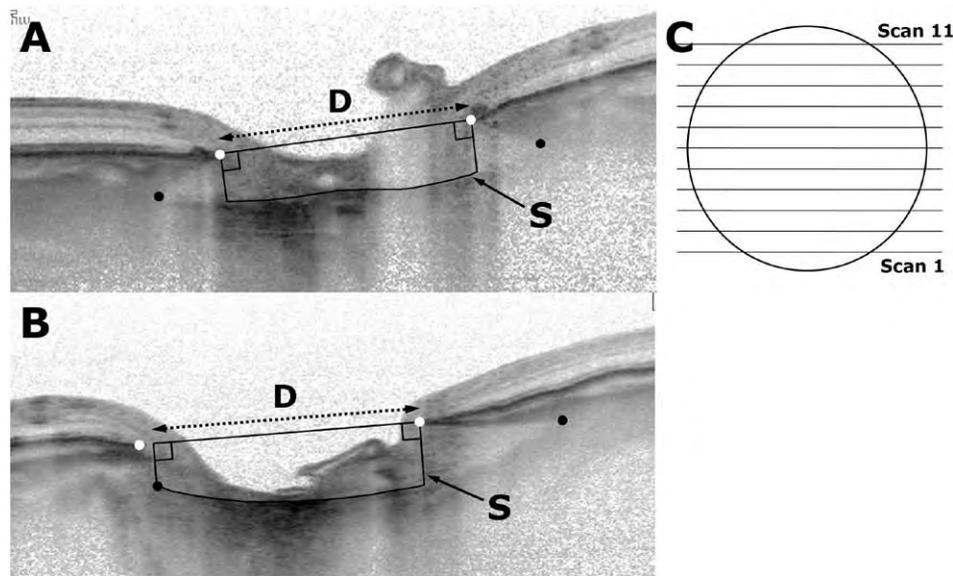
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Figure 1. (**A**, **B**) After delineating the anterior surface of the LC and the line connecting the two Bruch's membrane edges, the mean LC depth was approximated by dividing *area S* by *length D* for the LC area under the Bruch's membrane opening, 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 the most peripheral anterior LC point that could be identified with confidence, respectively. The *circle* in (**C**) indicates the Bruch's membrane opening. (**A**) and (**B**) are from glaucomatous eyes. Reprinted with permission from Furlanetto RL, Park SC, Damle UJ, et al. Posterior displacement of the lamina cribrosa in glaucoma: In vivo interindividual and intereye comparisons. *Invest Ophthalmol Vis Sci.* 2013;54:4836–4842.[22]

untreated IOP level, based on the discretion of two glaucoma specialists (JML and RR). Glaucoma patients were divided into three groups based on standard automated perimetry (Humphrey VF Analyzer, 24-2 SITA-Standard strategy; Carl Zeiss Meditec, Inc., Dublin, CA, USA): preperimetric glaucoma (no VF defects), mild-to-moderate glaucoma (VF mean deviation [MD] better than −12 dB), and severe glaucoma (VF MD worse than −12 dB). A glaucomatous VF defect was defined as a glaucoma hemifield test result outside normal limits on at least two consecutive VF tests or the presence on two consecutive tests of at least three contiguous test points within the same hemifield on the pattern deviation plot at $P < 0.01$, with at least one point at $P < 0.005$. These tests required reliability indices better than 15%. Glaucoma patients with characteristic optic disc and/or retina changes but without VF defects that meet these criteria were classified as having preperimetric glaucoma. All subjects provided a detailed medical and ocular history and underwent slit lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, dilated fundus examination, stereo disc photography (Stereo Camera 3-DX; Nidek, Inc., Palo Alto, CA, USA), standard automated perimetry, circumpapillary RNFL thickness measurement with a circular scan diameter of 3.46 mm, and serial horizontal and vertical EDI OCT B-scans of the optic nerve head (Spectralis HRA+OCT version 6.0.11.0; Heidelberg Engineering, GmbH, Dossenheim, Germany). Perimetry, disc photography, and OCT were performed within a 3-month period. Normal subjects were required to have normal-appearing open iridocorneal angles, IOP between 10 and 21 mm Hg, normal VFs, clinically normal optic discs, and no apparent ocular or systemic conditions that could affect the optic nerve.

We excluded eyes with previous posterior segment intraocular surgery, ocular trauma, systemic or ocular conditions other than glaucoma known to affect the optic nerve structure or VFs, visually significant cataract with best-corrected visual acuity of 20/40 or less, or poor quality EDI OCT images. We also excluded eyes with torted optic discs (the axis of longest disc diameter differed by >10 degrees from the vertical axis of the disc) because the LC structure in those eyes may be different from that in nontorted discs.

For EDI OCT of the optic nerve head, we used methods described in our previous reports.[25,26] Briefly, the OCT device was set to image a 15° × 10° rectangle for horizontal scans (and a 10° × 15° rectangle for vertical scans) centered on the optic disc. Radius of anterior corneal surface was measured using a keratometer (KR-8000PA; Topcon Medical Systems, Oakland, NJ, USA) and entered into the OCT device's built-in software. This rectangle was scanned with 97 sections (interval between images, approximately 30 μm), and each section had 20 OCT frames averaged. The EDI OCT images were obtained by selecting the EDI mode of the OCT device. Before automated EDI OCT mode of the OCT device was available, the EDI OCT images were obtained by pushing the OCT device closer to the eye to move the zero reference plane more posteriorly and create an inverted image (the inner portion of the retina shown facing downward). All EDI OCT images were obtained in a standardized dark room without dilation.

To determine the mean LC depth of each eye, we used the method described in our previous study.[22] Briefly, for one randomly chosen eye of each subject, 11 equally spaced, horizontal scans along the longest vertical diameter of the Bruch's membrane opening (Fig. 1C) were selected to delineate the anterior laminar surface and the line connecting the flanking edges of Bruch's membrane (line D in Fig. 1A). The longest vertical diameter of the Bruch's membrane opening was determined by reviewing serial vertical EDI OCT scans. The line D was used as a reference plane for LC depth measurement. Lines perpendicular to the reference plane at both flanking edges of Bruch's membrane were drawn to the anterior surface of the LC to create area S (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 most peripheral anterior LC point that could be identified with confidence, perpendicularly to the line connecting the two Bruch's membrane edges (Fig. 1B). The mean LC depth in each EDI

TABLE. Clinical Factors in the Normal, Preperimetric, Mild-to-Moderate (VF MD Better Than −12 dB), and Severe Glaucoma (VF MD Worse Than −12 dB) Groups

	Normal $N = 86$	Glaucoma			P Value*
		Preperimetric $N = 47$	Mild-to-Moderate $N = 55$	Severe $N = 60$	
Age, y	56 ± 14	60 ± 16	59 ± 16	59 ± 17	0.285
IOP, mm Hg	14.7 ± 2.1	15.7 ± 3.0	15.0 ± 3.3	14.3 ± 3.9	0.121
Average RNFL Thickness, μm	99 ± 11	86 ± 14	66 ± 11	52 ± 10	<0.001
Visual field mean deviation, dB	NA	NA	−6.0 ± 3.2	−19.7 ± 6.1	<0.001

Values are described as mean ± standard deviation. NA, not available.

* P values were calculated using one-way analysis of variance for age, IOP, and average RNFL thickness and using independent t-test for VF MD (all data were normally distributed; $P > 0.05$ by Shapiro-Wilk test).

OCT B-scan was determined by dividing area S by the length of line D. The mean LC depth of each eye was calculated by averaging the 11 mean LC depths from the 11 EDI OCT B-scans. All measurements were performed using ImageJ software (developed by Wayne Rasband, National Institutes of Health, Bethesda, MD, USA; 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. 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.

We recorded age and IOP at the time of EDI OCT and VF MD on the most recent VF test within 3 months of EDI OCT imaging. Mean LC depth of the eye was compared among the four groups (normal group and three glaucoma groups [preperimetric, mild-to-moderate, and severe glaucoma groups]) using one-way analysis of variance. In glaucomatous eyes with VF defects on standard automated perimetry (excluding normal subjects and preperimetric glaucoma patients), Pearson or Spearman correlation analysis was performed between mean LC depth and VF MD and between mean LC depth and average RNFL thickness. Mean age, IOP, and average RNFL thickness were compared among the four groups using one-way analysis of variance. VF MD was compared between mild-to-moderate glaucoma and severe glaucoma groups using independent t-test or Mann-Whitney U test. For all analyses, parametric or nonparametric tests were utilized based on the normality test. Statistical analyses were performed using the Statistical Package for the Social Sciences version 17.0 (SPSS, Inc., Chicago, IL, USA) and the level of statistical significance was set at $P < 0.05$.

RESULTS

Three hundred twenty-one eyes (321 subjects) met the entry criteria and had EDI OCT of the optic nerve head. Seventy-three eyes (73 subjects) were excluded because of poor quality EDI OCT scans or an incomplete set of serial EDI OCT scans. A total of 86 normal eyes (86 subjects, 46 women), 47 preperimetric glaucomatous eyes (47 subjects, 26 women), and 115 glaucomatous eyes with VF loss on standard automated perimetry (115 subjects, 61 women) were included. Glaucomatous eyes with VF loss were divided into two groups: 55 eyes with mild-to-moderate glaucoma (VF MD better than −12 dB) and 60 eyes with severe glaucoma (VF MD worse than −12 dB). All 162 glaucomatous eyes were under treatment to

lower IOP. Age, IOP, average RNFL thickness, and VF MD in each group are described in the Table. Mean age and IOP were similar among the four groups ($P = 0.285$ and 0.121, respectively). Average RNFL thickness was significantly different across all four groups ($P < 0.001$). There were 102 eyes with primary open-angle glaucoma, 30 eyes with exfoliative glaucoma, 15 eyes with pigmentary glaucoma, and 15 eyes with primary chronic angle-closure glaucoma. Ninety-two of 248 eyes (37%) had an LC feature seen in Figure 1B (externally oblique border tissue of Elschnig) in one or more of the 11 selected EDI OCT scans.

Mean LC depth was significantly greater in eyes with preperimetric glaucoma compared to normal eyes (390 ± 73 vs. 344 ± 66 μm, $P = 0.004$) and also in eyes with mild-to-moderate glaucoma compared to eyes with preperimetric (448 ± 93 vs. 390 ± 73 μm, $P = 0.001$). However, mean LC depth was similar between mild-to-moderate and severe glaucomatous eyes (448 ± 93 vs. 437 ± 114 μm, $P = 0.52$; Fig. 2A; one-way analysis of variance with post hoc tests). Mean LC depth of each of the 11 scans was plotted as an LC depth profile for each group (Fig. 2B; one-way analysis of variance with post hoc tests). Among groups, the LC depth profiles showed significant posterior displacement across all scans from normal eyes to eyes with preperimetric glaucoma and from eyes with preperimetric glaucoma to eyes with mild-to-moderate glaucoma ($P < 0.018$). However, no significant difference in LC depth was seen between mild-to-moderate and severe glaucomatous groups in any of the 11 scans ($P > 0.17$).

Finally, mean LC depths of 115 glaucomatous eyes with VF loss on standard automated perimetry (mild-to-moderate glaucoma and severe glaucoma groups) were plotted against their VF MD (Fig. 3A) and average RNFL thickness (Fig. 3B) with no significant correlation ($P = 0.56$ and 0.90, respectively, by Spearman correlation test). For all analyses, there was no change in statistical significance after controlling for age and IOP.

DISCUSSION

Along with focal laminar defects (laminar holes and laminar disinsertions), initial LC thickening and subsequent LC thinning,[6,9,15,23–26] posterior LC displacement is one of the characteristics of LC deformation in glaucoma.[7–12,17–22] Histologic studies using animal and human eyes[7–12] have shown posterior LC displacement to be associated with increased IOP or glaucomatous optic neuropathy. This has been confirmed by in vivo imaging studies on humans.[17–19,22] To utilize the anteroposterior LC position within the optic nerve head as a clinical parameter for monitoring glaucoma progression, its pattern of changes with worsening glaucoma must be determined. For example, a linear relationship between increasing LC depth and glaucoma severity would allow for meaningful
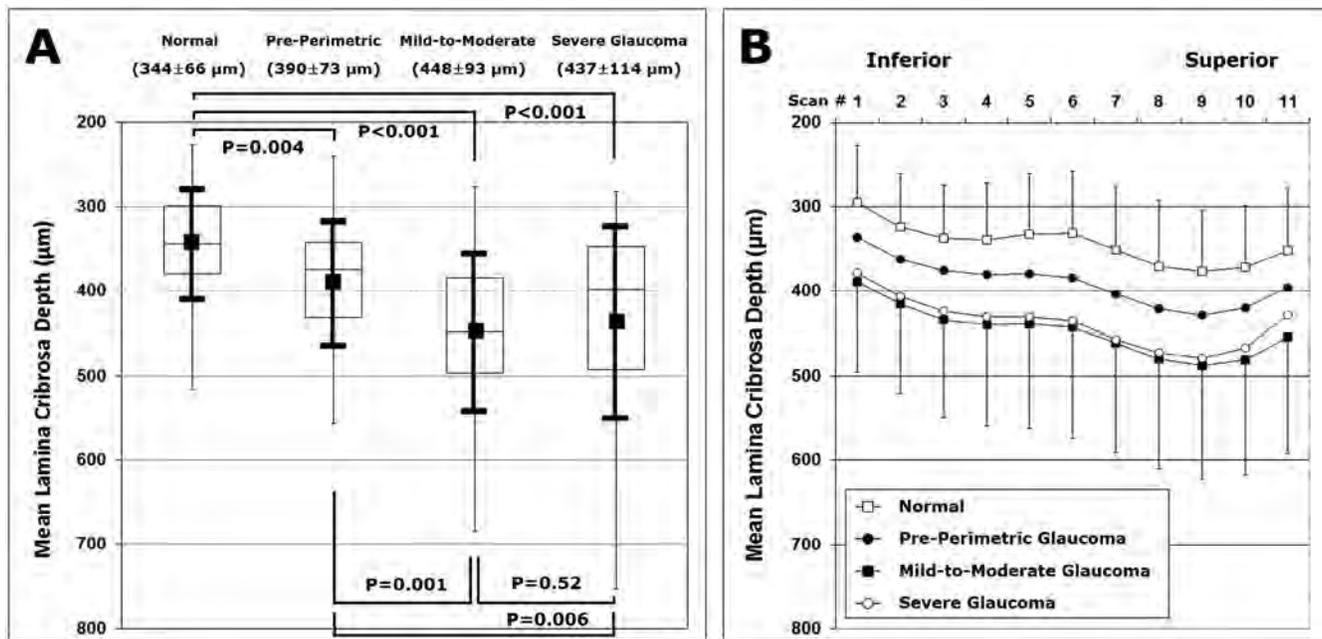
FIGURE 2. **(A)** Box-and-whisker plot of the mean LC depth of each group (average of the 11 mean LC depths from the 11 EDI OCT B-scans) measured from Bruch's membrane opening level in the normal, preperimetric glaucoma, mild-to-moderate glaucoma (VF MD better than −12 dB), and severe glaucoma (VF MD worse than −12 dB) groups. *Black squares*, *thick error bars*, and *thin error bars* represent means, standard deviations, and maximum/minimum values, respectively. **(B)** Mean LC depth profile in 11 horizontal EDI OCT scans (scan 1 → 11 = inferior → superior) in the four groups. In all 11 scans, the mean LC depth was significantly greater in the preperimetric glaucoma than in the normal groups, and in the mild-to-moderate glaucoma than in the preperimetric glaucoma groups ($P < 0.018$). However, there was no significant difference between the mild-to-moderate and the severe glaucoma groups in any of the 11 scans ($P > 0.17$).

assessment over the full range of disease. On the contrary, an asymptotic relationship would make LC depth analysis useful for only a certain range of disease, whether early or late stage.

In our previous study, LC depth was significantly greater in patients with glaucoma compared to normal subjects.[22] In that interindividual comparison, glaucoma patients had a range of

optic disc and VF abnormalities representing various stages of glaucomatous damage (VF MD range, −29.6 to −0.5 dB) but preperimetric glaucoma was not included in the analysis.[22] For a more detailed view of LC depth in glaucoma, the current study included eyes with preperimetric glaucoma and further divided the glaucomatous eyes with VF loss into two groups
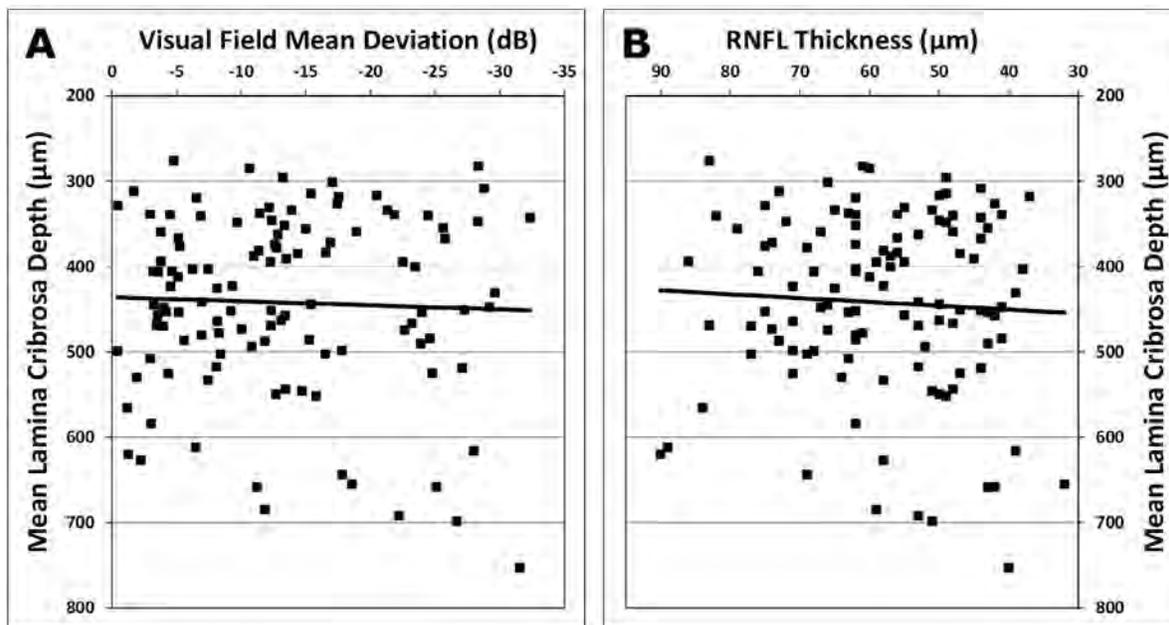

FIGURE 3. Scatter plots of mean LC depth versus **(A)** VF MD and **(B)** average RNFL thickness in 115 glaucomatous eyes with VF loss on standard automated perimetry (mild-to-moderate glaucoma and severe glaucoma groups), showing no significant correlation ($P = 0.56$ and 0.90, respectively).

(mild-to-moderate and severe) using a larger subject population. We demonstrated that posterior LC displacement was present in eyes with preperimetric glaucoma when compared to normal eyes. Further posterior LC displacement from the eyes with preperimetric glaucoma to those with glaucomatous VF loss was also significant. However, there was no significant difference in anteroposterior LC position between mild-to-moderate and severe glaucomatous eyes and there was no significant correlation between LC depth and VF MD or RNFL thickness in glaucomatous eyes with VF loss. Because our study is not a longitudinal study, we cannot create a time course model of LC depth versus disease severity. Nonetheless, the differences in LC position at different stages of glaucoma offers insight on the longitudinal pattern of LC position change, necessitating further investigation.

A reliable time course of posterior LC displacement could guide the usage of LC depth in glaucoma monitoring. Our results suggest the possibility of monitoring patients using LC depth for glaucoma development and its progression through the preperimetric and mild-to-moderate stages. Our results also suggest decreased utility of LC depth in monitoring patients after mild-to-moderate VF loss is detected in standard automated perimetry. Similarly, a potential treatment targeting the LC, especially an intervention for preventing posterior LC displacement, may be more effective if applied during the preperimetric stages of glaucoma when anteroposterior LC position is still changing.

Because we studied established glaucoma patients treated with various pressure lowering regimens, our results can only be applied to similar patients. In contrast to our result of no significant change in anteroposterior LC position between mild-to-moderate and severe glaucomas, histologic studies of primate eyes with experimental glaucoma[7–11] and of ex vivo human eyes[12] with artificially elevated IOP demonstrated progressive posterior LC displacement. Histologic studies of human donor eyes with a history of glaucoma[5,6] also demonstrated progressive posterior LC displacement. However, pressure-lowering treatments may alter the natural disease course and associated LC position change. In previous experiments using primate or ex vivo human eyes,[7–12] IOP was maintained at a constant elevated level. However, the IOP of our established glaucoma patients was maintained mostly within a statistically normal range with treatment, which may explain the lack of LC depth change in glaucomatous VF loss groups. Anecdotal clinical accounts of extremely deep disc cupping may be attributed to an extended period of untreated elevated IOP. Therefore, our results may not reflect anteroposterior LC position changes in untreated glaucoma.

Comparison of mean LC depth at 11 different sequential locations of the optic nerve head showed increased depth across all LC areas, which is consistent with our previous study.[22] These results suggest that the LC may undergo uniform posterior displacement in the early stage of glaucoma rather than a more dramatic, focal depression amidst areas of nondisplacement. However, these results should be interpreted cautiously as we could not evaluate the entire anterior LC surface. Although the 11 horizontal scans were spaced equally over a majority of the anterior LC surface, the superior and inferior LC insertion areas were excluded, as shown in Figure 1C. Additionally, nasal and/or temporal insertion areas were excluded in certain scans (Figs. 1A, 1B), because of poor visibility of the LC in those areas. Therefore, uniform LC displacement in the early stage of glaucoma can only be applied to its central and midperipheral areas.

Our results showing early posterior LC displacement and late LC depth stabilization do not imply a lack of LC injury in advanced glaucoma. Previous studies showed that focal LC defects in glaucoma, which may have a separate pathogenesis than posterior LC displacement, occurred preferentially in the LC insertion areas.[23,24] Also, eyes with greater glaucomatous VF loss had an increased number of focal LC defects.[23] Although speculative, our data suggest that the course of LC change in glaucoma could feature early uniform posterior LC displacement and accumulation of focal LC defects continuing until later stages, especially at the LC insertion. As expected based on Figure 2, correlation analysis between mean LC depth and VF MD in patients with glaucomatous VF defects showed no relation (Fig. 3A). Because RNFL thickness does not have a linear relationship with VF MD,[27] Figure 2 does not imply a lack of relation between mean LC depth and RNFL thickness. However, no correlation was found between these two parameters in patients with glaucomatous VF defects.

For best utilization of LC depth as a potential parameter for monitoring glaucoma development or progression, knowledge of the reversible and irreversible components of posterior LC displacement is important. The two components of posterior LC displacement have been demonstrated in previous studies.[5–7,17–19,28] The reversible component represents the stress on the LC at a given time and responds to IOP-lowering medications[17] and procedures[18,19] within a relatively short period of time. On the other hand, the irreversible component represents the accumulated damage to the LC as a result of chronic glaucomatous change. In our study, it was impossible to know what proportion of each LC depth measurement represented the reversible or irreversible component. By controlling for IOP, the variation in the reversible components between groups and, thus, its contribution to our results was minimized. Therefore, the observed LC depth differences among the groups likely represent the difference in irreversible components. This suggests that LC depth would be best used in treated glaucoma patients with stable IOP because these patients would have minimal variation in their reversible components. Neglected disease and severely elevated IOP would result in increased reversible LC displacement that could not be accurately accounted for by our model.

In addition to the aforementioned limitations, our study is limited by the intrinsic properties of OCT, particularly by decreasing sensitivity/signal strength with depth and its scanning speed. Because of these limitations, 73 of 321 eyes that met the entry criteria (23%) were excluded from analysis because of poor quality EDI OCT scans or an incomplete set of serial EDI OCT scans.

A reliable time course of LC depth as glaucoma advances could be used in monitoring disease progression. We demonstrated that anteroposterior LC position is different in different stages of treated human glaucoma with a significant posterior LC displacement observed in early stages before VF loss is detected in standard automated perimetry. These results suggest that LC depth may be most useful in early glaucoma through the preperimetric and mild-to-moderate stages. Further longitudinal studies are necessary to elucidate the sequence of such changes as glaucoma progresses from normal to preperimetric to mild-to-moderate to severe.

Acknowledgments

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