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Comparison between Lamina Cribrosa Depth and Curvature as a Predictor of Progressive Retinal Nerve Fiber Layer Thinning in Primary Open-Angle Glaucoma

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Purpose: To compare the ability of lamina cribrosa (LC) depth (LCD) and LC curvature to predict the rate of progressive retinal nerve fiber layer (RNFL) thinning in patients with primary open-angle glaucoma (POAG).

Design: Observational case series.

Participants: A total of 114 eyes of 114 patients diagnosed with POAG, in which RNFL thickness had been measured by serial spectral-domain (SD) OCT for at least 2.5 years.

Methods: The optic nerves of all participants underwent enhanced depth imaging volume scanning, and their circumpapillary RNFL thickness was measured using SD OCT, followed by regular serial measurements of RNFL thickness at intervals of $\geq$6 months. The LCD from the levels of Bruch's membrane (BM, LCD-BM) and the anterior sclera (AS, LCD-AS), and LC curvature index (LCCI) were measured by SD OCT at 3 locations: superior midperipheral, midhorizontal, and inferior midperipheral. The rate of RNFL thinning over time was determined by linear regression of serial OCT measurements of RNFL thickness.

Main Outcome Measures: Factors associated with the rate of OCT RNFL thinning.

Results: Univariate analysis showed that larger LCD-BM ($P = 0.001$), LCD-AS ($P < 0.001$), and LCCI ($P < 0.001$) were all significantly associated with a faster rate of global RNFL thinning. The LCCI showed a stronger correlation with the rate of global RNFL thinning than LCD-BM ($P < 0.001$) or LCD-AS ($P < 0.001$). Of the 3 variables, only LCCI remained significant on multivariate analysis ($P < 0.001$). Disc hemorrhage during follow-up ($P = 0.003$), wider parapapillary atrophy β-zone ($P = 0.017$), and greater global RNFL thickness ($P = 0.040$) were also significantly associated with a faster rate of global RNFL thinning.

Conclusions: Morphology of LC was significantly associated with the rate of progressive RNFL thinning. Curvature of LC better predicted progressive RNFL thinning than did LCD measured from the BM or AS. *Ophthalmology Glaucoma 2018;1:44-51 © 2018 by the American Academy of Ophthalmology*

Supplemental videos available at www.ophthalmologyglaucoma.org.

Posterior deformation of the lamina cribrosa (LC) is the principal event that induces axonal damage in glaucoma.[1-4] The LC deformation is thought to induce the death of retinal ganglion cells through various mechanisms, including blockade of axoplasmic flow and tissue remodeling by reactive astrocytes.[5-9] Recent experimental studies have shown that LC displacement occurs before detectable optic nerve damage.[2-4] The involvement of LC deformation and its occurrence before axonal damage in glaucomatous optic neuropathy suggest that LC morphology may predict disease outcomes.

Morphology of LC may be analyzed by various parameters. For example, LC depth (LCD) measured from the Bruch's membrane (BM) opening (LCD-BM) has been found to depend on intraocular pressure (IOP),[10,11] suggesting that LCD may be an indicator of IOP-related LC strain in glaucomatous eyes. Moreover, the LCD-BM was shown to be significantly associated with the rate of progressive retinal nerve fiber layer (RNFL) thinning in patients with primary open-angle glaucoma (POAG).[12] However, LCD-BM measurements include choroidal thickness, which varies among individuals.[13] Therefore, LCD-BM may provide an inaccurate assessment of LC strain. Recently, Vianna et al[14] suggested the anterior scleral (AS) opening as a more reliable reference structure to measure the LC position. The LCD measured from the AS opening (LCD-AS) may be more robust than LCD-BM because it is not influenced by the choroidal thickness.

Our group showed that the curvature of the LC, as assessed by the LC curvature index (LCCI), also may be a reliable parameter for evaluating LC morphology. We demonstrated that changes in LC curvature correlated with changes in IOP.[15] In addition, the LCCI performed better than LCD-BM in distinguishing between healthy and

https://doi.org/10.1016/j.ogla.2018.05.007
ISSN 2589-4196/18

glaucomatous eyes,[16] suggesting that LC curvature may better characterize LC deformation in glaucomatous eyes. More recently, we reported that the LCCI was associated with the rate of progressive RNFL thinning in glaucoma suspect eyes.[17]

Although several parameters have been described to assess LC strain, their relative accuracy and correlation with disease progression have not been determined. The present study compared the degree of association of LCD-BM, LCD-AS, and LCCI with the rate of progressive RNFL thinning in patients with primary open-angle glaucoma (POAG).

Methods

This investigation was a retrospective analysis of the data gathered from the Investigating Glaucoma Progression Study (IGPS), which is an ongoing prospective study of glaucoma patients at the Seoul National University Bundang Hospital Glaucoma Clinic, Seoul, South Korea. The study included consecutive subjects who met the eligibility criteria, all of whom provided written informed consent to participate. This study was approved by the Seoul National University Bundang Hospital Institutional Review Board and followed the tenets of the Declaration of Helsinki.

Study Subjects

Subjects who were enrolled in the IGPS underwent a comprehensive ophthalmic examination, including visual acuity assessment, Goldmann applanation tonometry, refraction tests, slit-lamp biomicroscopy, gonioscopy, dilated stereoscopic examination of the optic disc, disc photography (EOS D60 digital camera; Canon, Utsunomiyashi, Tochigiken, Japan), circumpapillary RNFL scanning, optic disc scanning (Spectralis; Heidelberg Engineering, Heidelberg, Germany), standard automated perimetry (Humphrey Field Analyzer II 750; 24-2 Swedish interactive threshold algorithm; Carl Zeiss Meditec, Dublin, CA), and measurements of corneal curvature (KR-1800; Topcon, Tokyo, Japan), central corneal thickness (Orbscan II; Bausch & Lomb Surgical, Rochester, NY), and axial length (IOL Master version 5; Carl Zeiss Meditec).

The IGPS excluded subjects with a history of intraocular surgery other than cataract extraction and glaucoma surgery, an intraocular disease (e.g., diabetic retinopathy or retinal vein occlusion) or a neurologic disease (e.g., pituitary tumor) that could cause visual field loss, and visual acuities worse than 20/40. All patients included in the IGPS were followed up every 3 to 6 months with regular follow-up fundus photography and spectral-domain (SD) OCT RNFL thickness was measured at intervals ranging from 6 months to 1 year. Patients included in the present study were required to be newly diagnosed with POAG, to have been followed up for at least 2.5 years with treatment, and to have undergone at least 5 serial OCT measurements. Primary open-angle glaucoma was defined as the presence of glaucomatous optic nerve damage (e.g., the presence of focal thinning, notching, and an RNFL defect), an associated glaucomatous visual field defect, and an open angle, as revealed by gonioscopy. A glaucomatous visual field defect was defined as (1) values outside the normal limits on the glaucoma hemifield test; (2) 3 abnormal points, with a probability of being normal of $P < 0.05$, and 1 point with a pattern deviation of $P < 0.01$; or (3) a pattern standard deviation of $P < 0.05$. Those visual field defects were confirmed on 2 consecutive reliable tests (fixation loss rate, $\leq$20%; false-positive and false-negative error rates, $\leq$25%).

Eyes with optic disc torsion of more than 15°[18] or a tilt ratio (minimum-to-maximum optic disc diameter) less than 0.75[19] and eyes with any abnormalities (including a large parapapillary atrophy [PPA]) in the circumpapillary region that affected the scan ring where the OCT RNFL thickness measurements were obtained were excluded from this study. A history of cataract surgery before the baseline examination was not an exclusion criterion in this study, but patients who underwent cataract surgery during the study were excluded because cataract extraction affects the signal quality of OCT scans and thus may influence the RNFL thickness data. Patients who underwent IOP-lowering surgery before or during the study also were excluded because the LC configuration may change substantially when the IOP re-elevates.[10,12]

Eyes also were excluded when a good-quality image (i.e., quality score >15) could not be obtained at more than 5 sections of enhanced depth imaging SD OCT disc scans (when the quality score does not reach 15, the image acquisition process automatically stops, and the image of the respective sections is not obtained). In addition, eyes were excluded when the images did not allow clear delineation of both the anterior and posterior borders of the central portion of the LC.

Untreated IOP was defined as the mean of at least 2 measurements before IOP-lowering treatment. The amount of IOP reduction was determined by calculating the percentage reduction of IOP at the final follow-up compared with the pretreatment level. The mean follow-up IOP measurement was obtained by averaging the IOP measured at 6-month intervals, and IOP fluctuation was determined using the standard deviation of these values.

A disc hemorrhage (DH) was defined as an isolated hemorrhage seen on the disc tissue or in the peripapillary retina connected to the disc rim.[20] A DH was detected by slit-lamp examination using a 78-diopter lens or a fundus photograph. Either of these was performed at every follow-up visit.

Enhanced Depth Imaging OCT of the Optic Disc

The optic nerve head (ONH) of each eye was imaged by Spectralis OCT using the enhanced depth imaging technique. The details and advantages of this technology for evaluating the LC have been described previously.[21,22]

Imaging was performed using a 10°×15° rectangle covering the optic disc. This rectangle was scanned with approximately 70 sections, which were 30 to 34 μm apart (the slicing distance is determined automatically by the machine). The average number of frames per section was 42, which provided the best trade-off between image quality and patient cooperation.[22] To enhance the visibility of the peripheral LC, all images were postprocessed using adaptive compensation.[23,24]

Measurements of Lamina Cribrosa Depth and Lamina Cribrosa Curvature Index

The LCDs and LCCIs on horizontal B-scan images were measured at 7 locations equidistant across the vertical optic disc diameter. These 7 B-scan lines, from the superior to the inferior regions, were defined as planes 1−7, respectively (Fig 1). In this model, plane 4 corresponds to the midhorizontal plane, and planes 2 and 6 correspond approximately to the superior and inferior midperiphery, respectively.

The LCD was measured both from the BM (LCD-BM) and the AS (LCD-AS). The reference planes of the BM and AS were determined on the basis of the peripheral BM,[14] which was defined as the location 800 μm from the BM opening (Fig 1). These reference points were chosen rather than the BM or AS opening, because the BM opening has been reported to migrate