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Optic Nerve Head Deformation in Glaucoma

A Prospective Analysis of Optic Nerve Head Surface and Lamina Cribrosa Surface Displacement

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Purpose: To evaluate long-term, longitudinal displacement of the optic nerve head (ONH) and anterior lamina cribrosa surfaces in glaucoma patients imaged with spectral-domain optical coherence tomography (SD OCT).

Design: Prospective study.

Participants: A total of 173 eyes of 108 subjects (88 with glaucoma and 20 normal subjects) followed for a mean of 5.3 years.

Methods: The optic disc was imaged with SD OCT at approximately 4-month intervals, and the ONH surface depth (ONHSD), anterior lamina cribrosa surface depth (ALCSD), and prelaminar tissue thickness (PTT) were measured. The reproducibility coefficients of ONHSD, ALCSD, and PTT were calculated from 2 baseline measurements of the glaucoma group. Change in ONHSD/ALCSD/PTT was confirmed when the differences between the first baseline and the latest 2 consecutive follow-up visits were greater than the corresponding reproducibility coefficient. Factors associated with ONHSD and ALCSD changes were identified with linear mixed modeling.

Main Outcome Measures: Proportion of eyes with ONHSD/ALCSD change.

Results: Within the glaucoma group, 23.9% (33 eyes) had confirmed ONHSD change (15.2% with posterior and 8.7% with anterior displacement) and 24.6% (34 eyes) had confirmed ALCSD change (12.3% with posterior and 12.3% with anterior displacement). Some 9.4% (13 eyes) showed a decrease in PTT, and 2.2% (3 eyes) showed an increase in PTT. The specificity for detection of ONHSD/ALCSD/PTT change was 91.4% (95% confidence interval [CI], 77.6-97.0), 82.9% (95% CI, 67.3-91.9), and 94.3% (95% CI, 81.4-98.4), respectively. There were no significant differences in the proportion of eyes with visual field progression or history of filtration surgery between the groups with anterior and posterior displacement of ONH/anterior laminar surfaces ($P \geq 0.678$). For each millimeter of mercury increase in the average intraocular pressure (IOP) during follow-up, the ONH and anterior laminar surfaces displaced posteriorly by 1.6 μm and 2.0 μm, respectively. An older age was associated with a decrease in magnitude of posterior displacement of the ONH and anterior laminar surfaces ($P \leq 0.009$).

Conclusions: The ONH and anterior laminar surfaces displaced not only posteriorly but also anteriorly (with reference to Bruch's membrane opening) in a significant portion of glaucoma patients. The magnitude of change was related to age and the averaged IOP during follow-up. *Ophthalmology 2015;■:1–13 © 2015 by the American Academy of Ophthalmology.*

Study of the optic nerve head (ONH) structures, including the lamina cribrosa (LC), is relevant to understanding the mechanisms of retinal ganglion cell degeneration in glaucoma and devising new diagnostic and therapeutic strategies. The advent of spectral-domain optical coherence tomography (SD OCT), adaptive optics optical coherence tomography (OCT), and adaptive optics confocal scanning laser ophthalmoscopy has improved the assessment of the LC and Bruch's membrane opening (BMO).[1–3] Although challenges remain in accurately delineating the posterior boundary of the LC and visualizing structures obscured by the retinal vasculature, SD OCT affords reliable measurement of the optic nerve head surface depth (ONHSD) and anterior lamina cribrosa surface depth (ALCSD), commonly defined by the perpendicular distances from a line joining the ends of BMO, or from the BMO plane fit in 3 dimensions, to the ONH surface and the anterior LC surface, respectively.[4–12] Strouthidis et al[5] demonstrated a significant increase in ALCSD over a mean follow-up of 2.8 months in 9 rhesus macaques induced with experimental glaucoma and proposed that ONH imaging and measurements would be useful in longitudinal follow-up of patients with glaucoma.[5] Clinical studies have demonstrated anterior displacement of the ONH and anterior LC surfaces after trabeculectomy[9–11] and posterior displacement of the

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ONH surface during acute intraocular pressure (IOP) elevation.[12] However, it remains unclear whether displacement of the ONH and LC surfaces can be observed clinically with serial measurements during the course of glaucoma progression. If present, moreover, it is unknown whether such displacement would be anterior or posterior. Current knowledge of deformation of the ONH and anterior LC surfaces in glaucoma is primarily derived from modeling[13–15] and experimental studies.[4–8] Therefore, a long-term clinical study is germane to address the nature of chronic, progressive deformation of the ONH in glaucoma. In this study, we analyzed the ONH imaged with SD OCT at approximately 4-month intervals in 173 eyes of 88 patients with glaucoma and 20 normal subjects followed for an average of 5.3 years. The objective of this prospective study was to investigate the longitudinal profiles of ONHSD/ALCSD and their association with IOP during longitudinal follow-up.

Methods

Subjects

A total of 132 subjects, including 93 with glaucoma and 39 normal healthy individuals, were consecutively enrolled and followed from March 2008 to September 2014 at the University Eye Center, the Chinese University of Hong Kong. After excluding 13 eyes of 13 patients with glaucoma and 43 eyes of 24 normal subjects because of indiscernible anterior LC surface in at least 1 B-scan in the baseline and follow-up visits (the presence of small optic cups or thick neuroretinal rim precluded the detection of the anterior LC surface, and more eyes were therefore excluded in the normal group), 138 eyes of 88 patients with glaucoma and 35 eyes from 20 normal subjects were included for analysis. All subjects had a complete ocular examination, including measurement of visual acuity, IOP, axial length, and refraction. Gonioscopy and fundus examination were performed. The optic discs were examined with slit-lamp biomicroscopy. Color optic disc stereophotographs were obtained. Included eyes had visual acuity $\geq$20/40 with longitudinal follow-up of at least 48 months. Eyes were excluded if there was evidence of macular disease, neurologic disease, and refractive or retinal surgery. Patients with glaucoma were identified on the basis of the presence of characteristic optic disc/retinal nerve fiber layer (RNFL) changes with corresponding visual field abnormalities in at least 1 eye, regardless of the level of IOP. Normal individuals had IOP $<$22 mmHg during all follow-up visits and no evidence of ocular disease, optic disc/RNFL abnormalities, or major systemic illness. Both eyes had optic disc and RNFL imaging with SD OCT, and visual field examination also was performed at the same visit at approximately 4-month intervals. Patients were managed during follow-up at the discretion of the attending ophthalmologists with reference to their target IOP. The study was conducted in accordance with the ethical standards stated in the 1964 Declaration of Helsinki and approved by local research ethics committee with informed consent obtained.

Optical Coherence Tomography Imaging

The optic disc was imaged with the Spectralis OCT (Heidelberg Engineering, GmbH, Dossenheim, Germany; super-luminescent diode laser center wavelength: 870 nm; scan speed: 40 000 A-scans per second) using 6 radial scan lines, each with 1024 A-scans, equally spaced at 30°. Because the study was initiated before the introduction of enhanced-depth imaging (EDI),[16] the baseline OCT scans were obtained without using the EDI mode. After June 2011, all OCT scans were then acquired using both EDI and non-EDI modes (both based on 6 radial scan lines). For this study, we included only non-EDI baseline and follow-up scans with clear visibility of the ONH and anterior LC surfaces. The RNFL was imaged with a circle scan comprising 1536 A-scans with a diameter of approximately 3.45 mm. The anterior and posterior boundaries of the RNFL were automatically segmented by the built-in software, and the global RNFL thickness was measured. Four eyes had RNFL segmentation errors, and the RNFL boundaries were manually edited by the instrument software. Both the radial scans and the circle scan were positioned at the optic disc center on the basis of the operator estimation of the clinical disc margin while the eye-tracking system was activated. Follow-up OCT scans were acquired with reference to the locations of the registered baseline scan using the eye-tracking technology. Fifteen B-scans at the same location were obtained and automatically averaged by the built-in software to increase the image signal-to-noise ratio. Averaging was applied to both radial and circle scans. All OCT volumes included in the study had a scan quality score of at least 20. The optic disc was also imaged with the Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA; super-luminescent diode laser wavelength: 840 nm; scan speed: 27 000 A-scans per second) at the same baseline visit using the optic disc cube scan (200 $\times$ 200 pixels) for measurement of the BMO area. The built-in software automatically detected the BMO in each of the B-scans and computed the BMO area. Cirrus HD-OCT BMO area measurement has been shown to have high repeatability.[17] All Cirrus HD-OCT RNFL analyses had a signal strength of $\geq$7 without any motion artefacts.

Measurement of Optic Nerve Head Surface Depth, Anterior Lamina Cribrosa Surface Depth, and Prelaminar Tissue Thickness

Measurement of ONHSD, ALCSD, and prelaminar tissue thickness (PTT) was performed in the Spectralis OCT B-scans using a customized computer program developed in Matlab (R2010a, the MathWorks, Inc., Natick, MA). All B-scans (1:1 pixel in scale) were exported as image files after setting the baseline scan as reference. The program measured the ONHSD, ALCSD, and PTT on manual detection and tracing of the BMO, internal limiting membrane, ONH surface, and anterior LC surfaces. The scaling factor (micrometers/pixel) for individual B-scans was extracted from the built-in software and applied in the customized program for calculation of ONHSD, ALCSD, and PTT. The tracing of the internal limiting membrane and ONH surface was assisted by the piecewise cubic Hermite interpolation polynomial (highlighted in green in Fig 1). The ONHSD (Fig 1B) represented the perpendicular distances from the reference line, a line joining the BMO (highlighted in pink in Fig 1), to the ONH surface (i.e., the perpendicular distances linking individual pixels of the reference line and the ONH surface were measured in the B-scan image [1024 $\times$ 496 pixels]). The ALCSD (Fig 1C) represented the perpendicular distances from the reference line to the detectable anterior LC surface (highlighted in orange in Fig 1), which was manually identified as the intersection between the horizontal moderate-intensity signal below the disc surface and the high-intensity vertical striations.[5] The PTT (Fig 1D) was the distance between the ONH and the detectable anterior LC surface (i.e., the differences between the ALCSD and the ONHSD along the detectable pixels of the anterior