Biomechanical Responses of Lamina Cribrosa to Intraocular Pressure Change Assessed by Optical Coherence Tomography in Glaucoma Eyes

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Submitted: December 18, 2016
Accepted: April 4, 2017

Citation: Quigley H, Arora K, Idrees S, et al. Biomechanical responses of lamina cribrosa to intraocular pressure change assessed by optical coherence tomography in glaucoma eyes. *Invest Ophthalmol Vis Sci*. 2017;58:2566–2577. DOI:10.1167/iovs.16-21321

Purpose. The purpose of this study was to measure change in anterior lamina cribrosa depth (ALD) globally and regionally in glaucoma eyes at different intraocular pressures (IOP).

Methods. Twenty-seven glaucoma patients were imaged before and after IOP-lowering procedures using optical coherence tomography. The anterior lamina was marked in approximately 25 locations in each of six radial scans to obtain global and regional estimates of ALD. ALD and its change with IOP were compared with optic disc damage, nerve fiber layer thickness, and visual field loss.

Results. Variables associated with deeper baseline ALD included larger cup/disc ratio, thinner rim area, larger cup volume, thinner central corneal thickness, and male sex (all $P \leq 0.02$). When IOP was lowered, ALD position became more anterior, more posterior, or was unchanged. The mean ALD change after lowering was 27 ± 142 μm ($P = 0.3$). The mean absolute value of ALD change was 112 ± 90 μm ($P = 0.002$). Change in ALD was greater in eyes with lower IOP in paired comparisons ($P = 0.006$) but was not associated with the magnitude of IOP lowering between imaging sessions ($P = 0.94$). Eyes with no significant change in ALD tended to have more visual field loss than those with significant anterior ALD displacement ($P = 0.07$). Areas within each optic nerve head that corresponded to zones with thicker nerve fiber layer had greater ALD positional change ($P = 0.0007$).

Conclusions. The lamina can move either anteriorly or posteriorly with IOP decrease, with greater displacement at lower IOP. Glaucoma eyes and regions within glaucoma eyes associated with greater glaucoma damage exhibited smaller responses.

Keywords: glaucoma, lamina cribrosa, optic nerve head, optical coherence tomography, intraocular pressure, biomechanics, stress

A major site of damage to retinal ganglion cell (RGC) axons in glaucoma is the optic nerve head (ONH), within the lamina cribrosa.[1–3] The biomechanical transmission of stress from intraocular pressure (IOP) produces strain in both the sclera and the ONH,[4–6] generating detrimental effects on RGC axons, ONH astrocytes, and nutritional blood flow in the nerve head.[7] The IOP level that produces RGC loss can be variable among individuals; some eyes suffer damage at IOPs that would be considered normal based on population studies, whereas many eyes with elevated IOP suffer no detectable damage. This suggests that the short- and long-term responses of scleral and ONH connective tissues to changes in IOP represent possible biomarkers for glaucoma incidence and progression. Normal lamina cribrosa structure is remodeled in glaucoma eyes, becoming deeper and wider[8] under the influence of a variety of factors, notably the stress of IOP as delivered through the sclera.[9] The regional differences in connective tissue density and pore size within the lamina cribrosa and greater regional strains suggest that the upper and lower poles of the ONH are weaker at resisting the stress of IOP in both human[10–14] and nonhuman primate eyes.[15] Indeed, these regions contain the axons of the RGCs most susceptible to glaucoma injury. In engineering models, the behavior of both the peripapillary sclera and the lamina cribrosa determine the effect of IOP.[16–18] Risk factors for human glaucoma include features of corneoscleral anatomy or physiology, including axial myopia, corneal hysteresis, and corneal thickness.[19] In human eyes with glaucoma, the sclera is stiffer by in vivo indirect measurement[20] and by ex vivo inflation testing[21] and undergoes alterations in collagen fiber orientation.[22] Optical coherence tomography (OCT) permits high-resolution imaging of the retina, choroid,[23] sclera, and ONH.[24] It may be possible to therapeutically alter the ocular mechanical response to IOP to benefit those with glaucoma,[25] as has been shown in mice.[26]

The aging ONH has more collagen[27] and smaller pores[28] for passage of axons, possibly contributing to the greater prevalence and progression of glaucoma in the elderly. Laser scanning microscopy,[29] small angle light scattering,[30] and wide angle x-ray scattering[31] of human eye tissues have elucidated lamina cribrosa structure and its response to induced displacement.[32] Chronic experimental IOP elevation in monkeys indicates that the ONH remodels to produce thicker beams, smaller pores,[33] and deeper

lamina.[34–37] Some investigations have attempted to measure the anterior and posterior borders of the lamina by spectral-domain OCT (SD-OCT), suggesting a thinner lamina in glaucoma eyes.[38–41] Indeed, the lamina is thinner in damaged glaucoma eyes by scanning electron microscopy.[42] However, the posterior lamina border is difficult to identify in OCT images,[43] whereas the position of the anterior lamina provides a recognizable, contrasting border that delineates it from the prelaminar tissues, which consist mostly of axons and astrocytes.[44] Thus, anterior lamina cribrosa depth (ALD) can now be quantitatively imaged by OCT.

ALD has been estimated in OCT images by marking one point or only a few locations at its "maximum depth below the opening of Bruch's membrane (BM)."[45,46] These studies found a deeper ALD in men and in eyes with shorter axial length. One investigation found deeper ALD with greater visual field loss in glaucoma patients, but no effect of age alone.[47,48] The baseline ALD is of less interest as a prognostic biomarker for glaucoma susceptibility than its dynamic mechanical properties. Human glaucoma eyes were stiffer by indirect clinical measures[49] and exhibit steeper stress—strain behavior in post mortem studies of the ONH[50] and sclera.[51] Likewise, experimental IOP elevation in monkeys produces a stiffer mechanical response in the sclera.[52,53] The peripapillary sclera has a circumferential pattern of collagen and elastin,[54] whereas the laminar fibers run generally directly across the nerve head, side to side.[55] These patterns are protective features that resist strain and their configuration is disturbed in glaucoma eyes.[56–58] Deepening of the lamina is observed with imaging the ONH of monkey eyes with acute IOP elevation.[59] There is a reduction in the depth and width of the optic disc cup on IOP lowering, particularly in younger eyes.[60–65] However, some imaging studies of disc change with IOP lowering were limited because they studied the effects of IOP change by measurement of disc surface topography alone,[66,67] which, while useful, is confounded by the coincident response of prelaminar axonal and glial tissues.[68]

We measured ALD change with change in IOP to determine the mechanical response of the sclera and ONH relative to glaucoma susceptibility. Past research has not used detailed analysis of regional lamina cribrosa behavior after IOP lowering. Nor have measures at multiple IOP levels from the same patient been used to simulate the modeling of an IOP deformation relationship for ALD. Comparison of regional laminar response to corresponding local axon damage could reveal features associated with inherent susceptibility. Furthermore, such study could delineate details of the postinjury remodeling of the ONH. We developed methods for regional analysis of the ONH in glaucoma eyes that were imaged at different IOP levels for comparison to important aspects of their glaucoma. This investigation presents, for the first time, estimates of change in regional lamina cribrosa position with change in IOP.

Methods

Patients

Adult glaucoma patients of the Wilmer Glaucoma Center of Excellence were imaged at standard visits. These patients were chosen in anticipation that their IOP was to be altered either medically, surgically, or by laser suturelysis after trabeculectomy. Some image sets were acquired on the same day at two IOP levels, whereas others were taken on separate days, with the majority separated by less than 1 month (see Results). Glaucoma was defined as reported in a standard definition system.[69] The study was approved and monitored by the Institutional Review Board of the Johns Hopkins School of Medicine, written informed consent was obtained, and the study abided by the Declaration of Helsinki.

Visual field parameters from HFA2i 24-2 field tests and OCT parameters from Cirrus OCTs of the ONH region (both from Carl Zeiss Meditec, Inc., Dublin, CA, USA) were obtained from testing performed for clinical visit purposes within 6 months of the acquisition of Spectralis (Heidelberg Engineering, Heidelberg, Germany) OCT images of ONH. Spectralis images were used to calculate ALD. In addition, we recorded age, race, sex, corrected visual acuity, type of glaucoma, glaucoma eyedrop treatment, central corneal thickness (CCT), and diabetes diagnosis. Only one eye of each of 27 persons was included.

At each imaging session, the axial length and keratometry measurements were taken with the IOL Master instrument (Carl Zeiss Meditec, Inc.). Keratometry readings and the most recent refraction were entered into an integrated patient database software (Heidelberg Eye Explorer; Heidelberg Engineering) to estimate optical magnification and therefore to allow for more accurate comparisons across individuals. IOP was measured immediately prior to each imaging session. IOP was obtained using the ICare tonometer (ICare Finland Oy, Espoo, Finland). We used the average of two mean measurements of six IOPs each. IOP had first been measured by applanation tonometry in each person to assure the accuracy of the ICare measurement.

The coordinator who performed OCT testing was not masked to the IOP level of research subjects, but in all subsequent steps, including the image analysis, the investigators were masked to all identifiers.

OCT Centered on the Optic Disc

For each patient at a given IOP, optic disc images were taken as six high-resolution radial sectors, therefore including each hour of the clock (Fig. 1) with 30° between each, averaged from 6 B-scans with 1024 A-scans per B scan acquired with a scanning speed of 40,000 A-Scans per second and 25 B-scans per second. The images were acquired in the mode called enhanced depth imaging to capture data from deeper than the retinal plane. All selected images, as well as the scaling factor correcting for magnification, were exported from the SD-OCT. Because the images had a fixed size, but different optical magnifications, the micrometer per pixel scale was different in the width dimension for each image. To analyze the images uniformly, the images were rescaled to a unified scale using image editing software (Photoshop CS5; Adobe Systems, Inc., San Jose, CA, USA). The images were then deidentified, so that the image grader was masked to the identity and diagnosis of the subject and which was the higher and lower IOP during analysis using a Java-based image processing software (ImageJ; National Institutes of Health, Bethesda, MD, USA).[70] On each radial sector image, points were marked at the position of the edge of BM on either side of the disc and along BM away from the nerve head for several points. Then, points were marked at the anterior lamina (AL) in approximately 25 locations per scan. Each of these points was given (x,y) coordinates in millimeters, with the lower left portion of the image as (0,0).

To measure positional changes in optic nerve head tissues, it is necessary to have a reference position against which to judge change. ALD was assessed by reference to the position of BM opening in each image, We constructed a line joining the (x,y) positions of the two end points of BM and calculated the distance in the optical axis from this line to positions every 0.1 mm along the fitted position of the AL (see below for fitting procedure). Recent clinical investigations have documented that the end position of BM at the disc is the most reliable biomarker for the entry point to the nerve head.[71–73] It is known that the first 2 mm of BM around the nerve head can

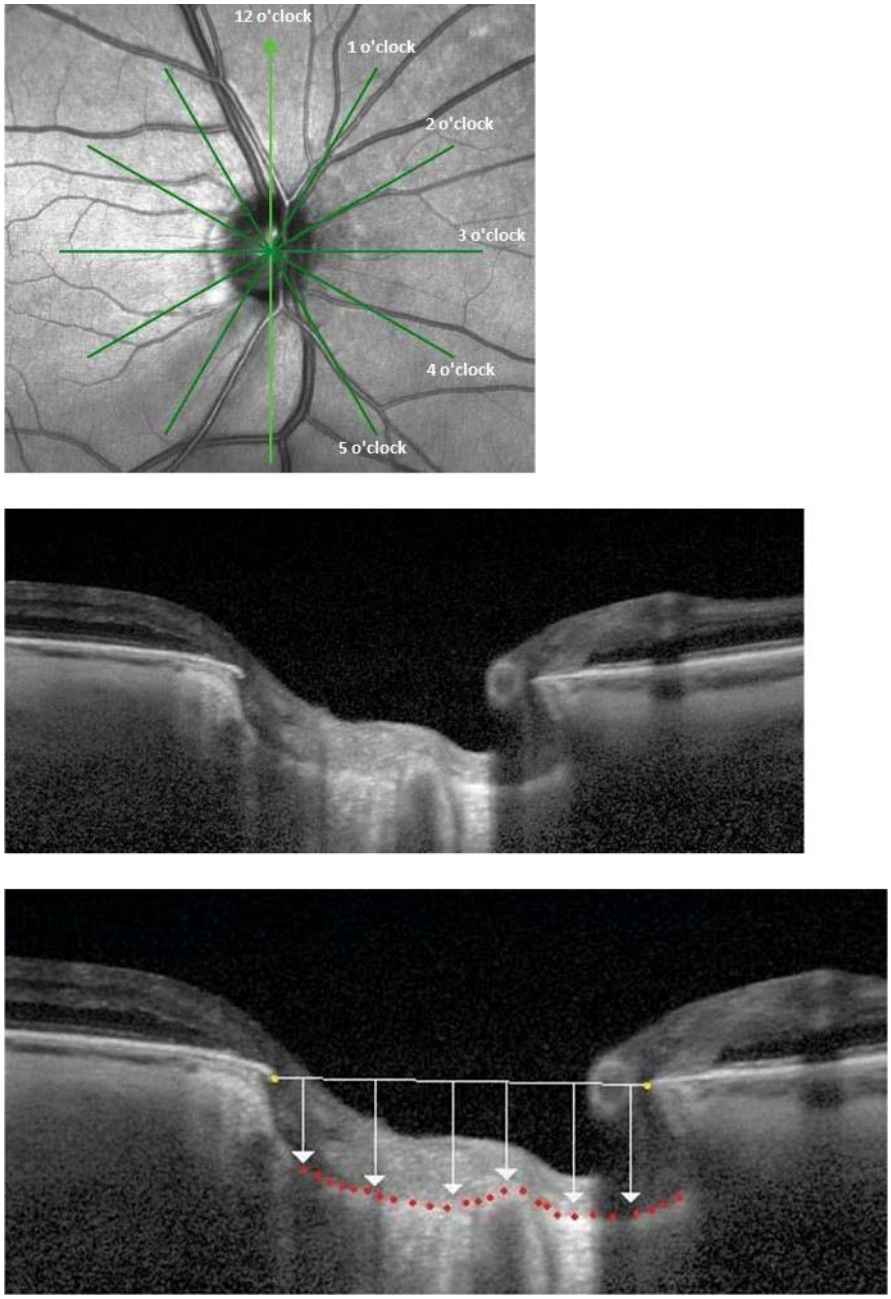


Figure 1. *Upper image* shows the position of the six radial OCT scan positions marked in *green*. An example scan is shown (*middle*) and the image is marked (*below*) at the ends of Bruch's membrane and a line connecting the two ends of Bruch's, markings of the anterior lamina cribrosa position (*red dots*) and the calculation of anterior lamina depth shown by *arrows*.

change shape with change in IOP or cerebrospinal fluid pressure[74] and the elasticity of BM decreases with older age.[75] Axial length and choroidal thickness (CT) change with IOP, so presumably the overall position of BM opening moved with IOP change, but in the Results we show that there were no significant changes in BM opening diameter in our data. Thus, although the position of BM opening moved anteriorly or posteriorly with change in IOP, this was not included in our measurements, which calculate the relative position of the AL from BM opening.

The ALD data from each of six radial scans was fit to a sixth-order polynomial function, which allowed sector by sector comparisons of data at the two IOPs, because it cannot be reasonably assumed that the points are marked at the identical locations along the AL in the two scans. In general, the r^2 values for these sixth order fits were well above 0.9. The curve fitting procedure provided estimation of some ALD positions that were blocked by overlying retinal blood vessels. We calculated the mean and median ALD and the depths of various regional portions of the lamina. We compared the ALD data at the lowest measured IOP to that from a higher IOP in each scan at points every 0.1 mm along the AL. In some patients, we acquired image sets at either three or four different IOP levels, and the values at higher IOP were compared for each patient to that taken at the lowest IOP.

To determine a difference between the ALD at two IOP levels in the same person, the direction of the change, "plus" or "minus," could be artibrarily set either way. We decided that

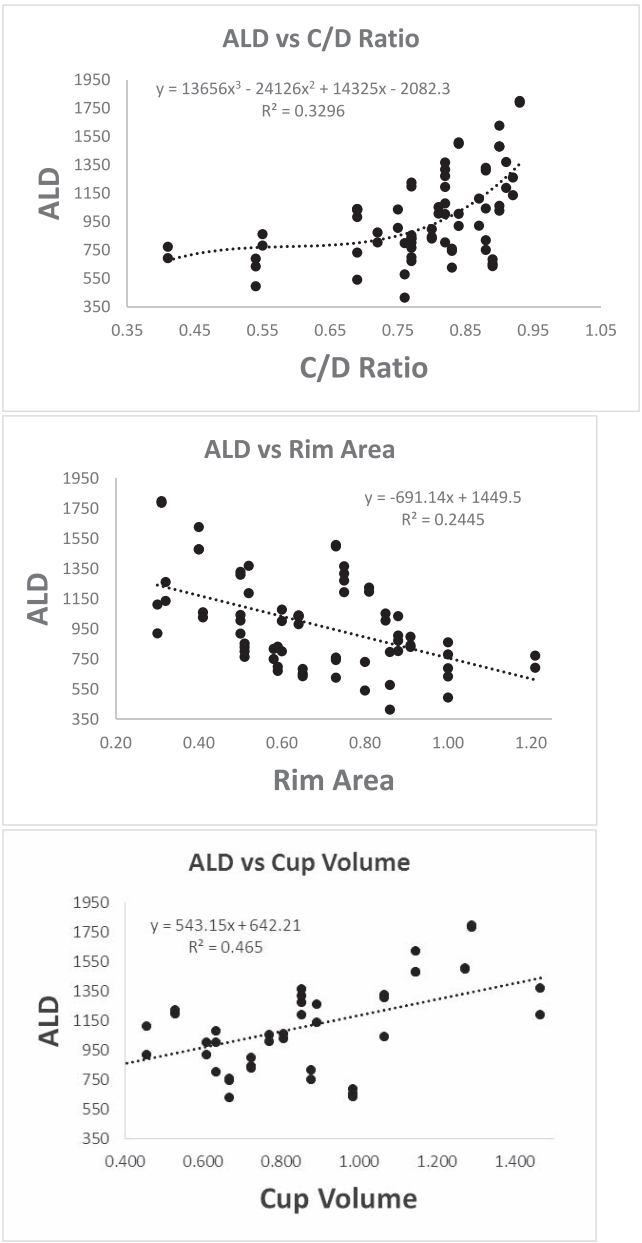


Figure 2. The ALD depth in micrometers was significantly related to cup/disc ratio, disc rim area, and cup volume.

a positive value of ALD change would indicate that the ALD value was larger (deeper, or further out of the eye) at the higher IOP level than at the lower IOP. A negative value of ALD change would occur when the ALD was closer to the vitreous at the higher IOP level and deeper at lower IOP. In addition to the mean ALD overall, we did regional calculations including the following: upper versus lower half of the nerve head; central versus peripheral (using the central 50% of area); and quadrant data grouping as 11, 12, and 1 o'clock (superior), 2, 3, and 4 o'clock (nasal in the right eye), 5, 6, and 7 o'clock (inferior), and 8, 9, and 10 o'clock (temporal in the right eye). We also calculated the ALD for each clock hour of the ONH. For comparisons among subjects, left eye data were converted to right eye format.

We calculated the diameter of BM opening in each radial scan, as well as the position and area of BM opening. Of 33 subjects from whom we initially collected scans, the ALD data for 6 eyes are not included here, because the quality of their images was insufficient to identify landmarks properly in one or both IOP levels, leaving data for 27 eyes of 27 patients to comprise the report. From some patients, we were able to measure the patient at three or four different IOP levels, giving 42 ALD observations overall.

To estimate the interimage variability in our overall measurement system, images of two eyes were taken at the same IOP each on separate measuring sessions and analyzed in masked fashion. One of these eyes had moderate glaucoma damage and one severe damage (mean deviation [MD] in field tests: –6.31 and –29.34, respectively). The average difference between ALD meassurements for these eyes was –23 μm (negative direction = shallower). In evaluating the change among eyes measured at different IOP levels, we consider twice this mean reproducibility or approximately 50 μm to represent an estimated limit for true change.

For each patient, the degree of glaucoma damage was judged from two separate measurements: data from Cirrus optic disc and nerve fiber layer imaging and a 24-2 visual field test. Cirrus OCT data were not used in calculating ALD. The Cirrus tests were performed within a mean of 5.1 months of the initial image sets of the disc or choroid/sclera, whereas the fields were performed within a mean of 6.3 months of the initial image sets. For regional comparisons within the optic disc, each clock hour and quadrant of Cirrus NFL data (from centroid of disc outward) was compared with the corresponding depth data from the center of the lamina to the disc perimeter in the the same clock hour. To compare ALD clock hour data to visual field test points, the value of the pattern deviation probability for each point was coded as an integer, rated proportional to its relative propability of abnormality: $P < 0.5\% = 10$, $<1\% = 5$, $<2\% = 2$, $<5\% = 1$, and $>5\% = 0$, in a method designed after that used in the Glaucoma Hemifield test. Those points that fell within a zone attributed to RGCs whose axons entered the disc in a particular clock hour were taken from a map of this correspondence reported by Garway-Heath et al.[76] These zones contained from 4 to 13 visual field test points per zone, and the sums of their coded probability values per region of the disc were compared.

Statistical Analysis

The primary outcome variable was change in ALD or ALD change between two different IOP levels. We also evaluated baseline and change in BM diameter. We explored the relationship between ALD and ALD change compared with parameters such as age, sex, race, severity of visual field damage, glaucoma diagnosis, glaucoma treatment, CCT, and baseline axial eye length. We used linear and multivariable regression analyses. We also used the Wilcoxon signed-rank test to assess the effect of nonparametric parameters. For the ONH data, the dependent variable was ALD and all estimates, and *P* values were derived from generalized estimating equation models that take into account correlations among repeat measurements of ALD for a single subject. Based on Akaike's information criterion for several plausible correlation structures, the correlation was assumed to have a first-order autoregressive structure, in which observations taken at closer IOP levels are more correlated. The same models were used for dependent variable change in ALD, but the correlation was assumed to have a compound symmetry structure, in which any two repeat observations from a subject have the same correlation. This was needed as we had two or three pairs of IOP levels, each with its ALD value, for some patients. When the dependent variable was change in ALD from lowest to highest IOP (that is, one comparison per subject with the extreme values of IOP), all estimates and *P* values are derived

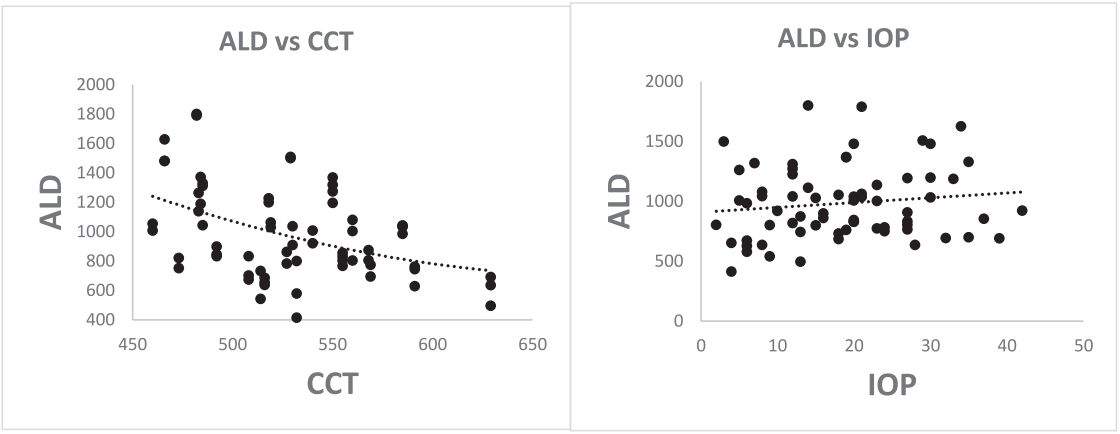


FIGURE 3. The ALD was deeper in eyes with thinner CCT, but ALD was not significantly related to the baseline level of IOP. Dotted lines are regression relationships; see text for statistical significance of relationships.

from general linear models because there is only one observation of change in ALD for each subject. ALD change data for the 27 eyes were divided into three equal-sized groups of 9 eyes each, consisting of those with larger positive ALD change (deeper at the higher IOP level), those with minimal change, and those with larger negative difference (deeper at the lower IOP level). Statistical testing for these data used the Kruskal-Wallis test for continuous factors or the Fisher-Freeman-Halton exact test for binary factors. All statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

ALD Level

Images of the ONH to assess ALD were obtained in 27 eyes with a total of 69 images. There were 42 pairs of comparisons of two IOP levels: 15 eyes had images at two IOP levels (one pair), 9 eyes had three different IOP levels with images, and 3 eyes had four IOP levels imaged. The mean number of marked points within the ALD in each of the six images in a set was 24.3 ± 5.3, for a mean of 145.6 marked locations in the average lamina overall ($n = 69$ nerve head images × 6 radial scans per image = 414 radial images).

The mean age was 69.7 ± 11.0 years, 14 of 27 were male, 18 were European derived, 5 were African derived, 3 were Asian derived, and 1 was of mixed derivation. Fifteen of 27 were pseudophakic, 25 of 27 were diagnosed as open angle glaucoma (2 were angle closure), only 4 were taking IOP-lowering eyedrops at the time of testing, and 2 were taking medication for diabetes or had diagnosed diabetes. Mean axial length was 24.6 ± 1.1 (range, 22.6 to 27.0). Twenty-six of 27 eyes had a change in IOP that resulted from postoperative suturelysis after trabeculectomy. The remaining eye had measurements before and after laser trabeculoplasty. The mean CCT of the 27 eyes was 526 ± 42 μm. The mean lowest IOP was 10.8 ± 5.9 (range, 2 to 23) mm Hg, whereas the mean change in IOP was 15.9 ± 7.8 (range, 4 to 29) mm Hg. The mean ALD for the 27 eyes at the lowest IOP level for each eye was 0.98 ± 0.33 mm (median, 0.92 mm).

In the initial analysis of ALD, we used every image from each subject, with models that accounted for intrasubject correlation. Mean ALD was 984 ± 305 μm for the 69 observations in 27 subjects. Mean ALD in these models was highly related to ONH parameters: average cup/disc ratio, rim area, and cup volume in Cirrus OCT images of the eyes collected separately (P values from linear regression: 0.005, 0.006, and <0.0001, respectively; Fig. 2). In each case, the more abnormal was each of the glaucoma damage parameters, the deeper the ALD.

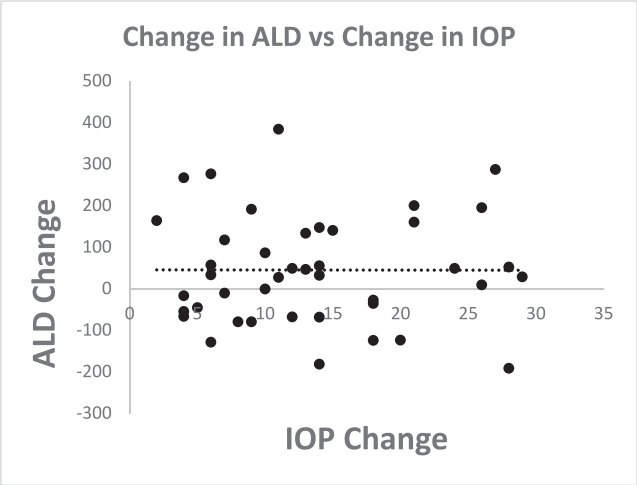
The ALD was not significantly related to the estimated number of axons in the ONH as judged by the overall NFL thickness or to the visual field indexes VFI and MD (P values from linear regression, 0.23, 0.22, and 0.28, respectively).

Several other parameters were related to the ALD value, including CCT, sex, and race. The thinner the CCT, the deeper the ALD (regression coefficient: –3.43 [CI: –6.17, –0.69], $P = 0.02$; Fig. 3). ALD was deeper in men (images analyzed include 35 images from men and 34 from women; regression coefficient for men = 274.8 [CI: 56.2, 493.5] and for women = 0 [reference]; $P = 0.02$). ALD was deeper in nonwhite persons (regression coefficient: –240.0 [CI: –483.4, 3.4] for whites [reference = nonwhites]; $P = 0.05$). The ALD was not significantly related to age, disc area, or the IOP level itself (e.g., for IOP level, regression coefficient = 0.27 [CI: –2.76, 3.31]; $P = 0.86$). These conclusions were the same, but still statistically significant, when we considered for each patient only the values for the image taken at the lowest IOP for that patient or the highest IOP for that patient (data not shown).

Change in ALD With IOP Change

The mean difference in ALD was 27 ± 142 μm for the 27 IOP pairings with the greatest difference between the two IOPs in each patient and 45 ± 132 μm for all 42 IOP pairs. These mean change values do not differ significantly from no change (one-sample t-test, $P = 0.3$). However, it was clear that there was a substantial number of eyes in which the lamina was more anterior (closer to the vitreous) at the higher IOP level than at the lower IOP (negative ALD change as defined here; Fig. 4). When we calculated the absolute value of the change in ALD, the mean displacement in ALD was 107 ± 88 μm for all pairings ($N = 42$, median = 75 μm) and 112 ± 90 μm for the change in ALD for the 27 pairs with the greatest difference between low and high IOP (median = 80 μm). These values indicated a statistically significant change in ALD from no change (t-test, $P = 0.002$).

In an initial analysis, we found that change in ALD on moving from a higher to a lower IOP was not significantly related to the absolute value of IOP change across all 42 pairings (coefficient: 0.14 [CI: –3.98, 4.26]; $P = 0.94$; Fig. 4, right graph). Rather, it was significantly related to the level of IOP in the lower IOP of the pairing—that is, change in ALD



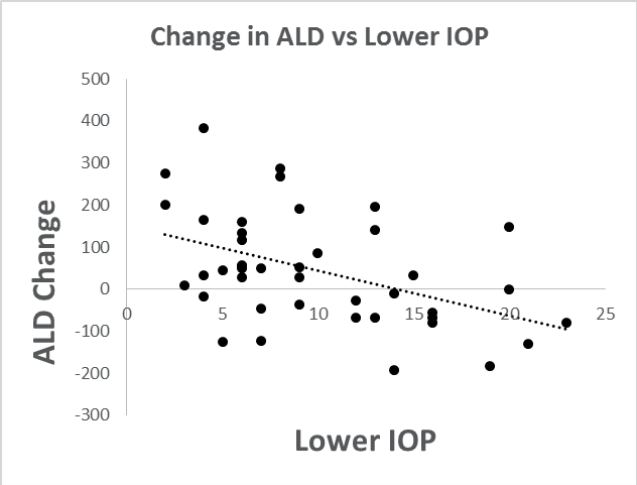


Figure 4. Change in ALD is not significantly related to the change in IOP (*left graph*) but is significantly greater at lower IOP than at higher IOP (*right graph*).

was greater (positive value) when the lower member of the IOP pairing was lower than when it was higher (coefficient: −11.30 [CI: −19.14, −3.46]; $P = 0.006$; Fig. 4, left graph). This relationship remained significant when we considered only one pair of IOP image sets per eye, using the lowest IOP and the highest IOP for each person ($n = 27$, coefficient, −10.53 [CI: −19.45, −1.61]; $P = 0.02$). The level of IOP at the lowest value for each subject was not significantly related to the change in IOP value ($P = 0.25$, linear regression). ALD change was not significantly related to the percent change in IOP (using the higher of the two IOP as the denominator for IOP change ($P = 0.08$, mixed model; Supplementary Table S1; Supplementary Fig. S1).

In Figure 4, these initial findings demonstrate that a substantial number of the ALD changes were in the direction defined as negative: with IOP decrease, the ALD became deeper (i.e., the lamina moved out of the eye at lower IOP). This substantial number of eyes moving in the wrong direction has a distinct impact on assessment of the average movement of the lamina. Their magnitude of change in most cases is several times the intrasubject variability and is thus not an artifact.

Mean ALD change was not related to age, CCT, disc area, rim area, cup volume, lens status, axial length, mean nerve fiber layer thickness, visual field index, MD, or PSD of field tests. The range of axial lengths in our study eyes did not include the extreme values of either highly hyperopic or myopic eyes.

Table 1. ALD Change Grouped by Direction of Movement

	Negative	Neutral	Positive
ALD difference (μm)	−192 to −68	−55 to 49	52 to 384
Cup volume (mm^3)	0.46	0.77	0.61
Visual field index	89	68	70
Mean deviation (dB)	−4.1	−12.9	−11.4
Pattern SD (dB)	7.20	11.06	9.74

N, 9 in each group.

Men had significantly deeper ALD overall than women. Similarly, nonwhite patients had deeper ALD, but exhibited ALD change similarly to whites with change in IOP ($P = 0.11$). Use of the absolute value of ALD change did not alter any of these associations significantly. The time interval between image sessions at the two IOP levels was not significantly related to the change in ALD ($N = 42$ pairs of observations; regression coefficient = –0.23 [CI: –0.52, 0.06]; $P = 0.11$). Of the 42 paired comparisons, 13 had imaging at the two IOPs on the same day, 17 were greater than 24 hours but less than 1 month, 9 were spaced from 1 month to 5 months, and 3 were at 18 months apart.

Change in ALD Grouped by Direction of Movement

Because ALD in some eyes moved in a negative direction, that is, ALD was deeper at lower IOP, we performed an analysis to determine whether taking into account the direction of motion, positive or negative, would alter the interpretation of the outcome, including features of patients related to the behavior of their ALD. We categorized the patients into three groups of equal size (nine eyes each) based on the direction that the lamina moved with IOP change: (1) those that moved in a negative direction (ALD was deeper at lower IOP), (2) those that had no defined ALD change, and (3) those that moved in a positive direction (ALD was deeper at higher IOP) (Table 1). The no change group had ALD difference values within intrasubject reproducibility (≤50-μm mean difference in either direction). There was no significant difference in the three groups in the degree of IOP difference between imaging sessions (median = 14 mm Hg in each group; $P = 0.71$, Kruskal-Wallis test). Comparison across the three groups indicated that the negative group had the most normal values of cup volume and visual field findings, whereas the neutral group, with the least change in ALD, had the worst cup volume and field damage (group differences, $P = 0.1$, Wilcoxon rank sum).

When the change in ALD was compared with MD in field, ALD change was greater for those with less field damage (in either the positive or negative direction) and converged on minimal ALD change with severe field loss (Fig. 5; ALD change presented as absolute value). The mean ALD change (absolute value) for eyes with MD better than –10 dB was 144 ± 103 μm ($n = 15$), whereas for those with MD worse than −10 dB, ALD change was half as large (78 ± 80 μm; $n = 12$, $P = 0.07$).

Regional Mean ALD and Change in ALD Data

To test whether the degree of glaucoma injury as judged by NFL thickness was related to ALD change, we matched the NFL thickness in each clock hour (Cirrus OCT) to the ALD change seen in each clock hour from the center of the disc to its rim (Spectralis OCT). There was a significant association between the ALD change in each clock hour and the peripapillary NFL thickness in that subject for the same clock hour (Table 2).

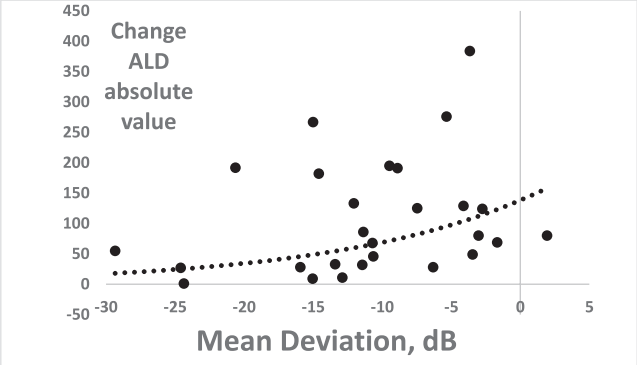


Figure 5. Mean deviation in field compared with ALD change (absolute value), one IOP pairing per subject, exponential fit of data in dotted line.

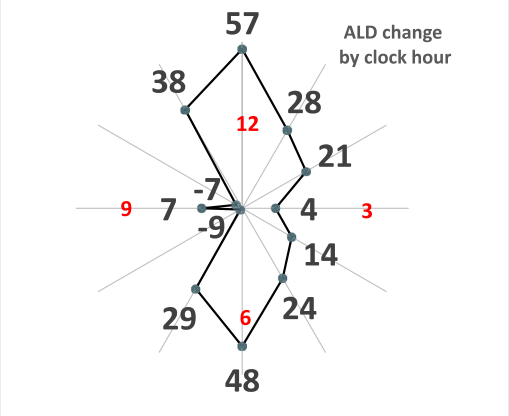


Figure 6. Mean change in ALD by clock hour, from center of the ONH to its periphery shows tendency for greater ALD change in the vertical meridians (*red numbers*, clock hours; *black numbers*, mean ALD depth change).

Regions within an ONH with greater NFL thickness had greater change in ALD ($P = 0.0007$; Table 2). The mean change in ALD depth by clock hour showed that ALD depth change was at least three times greater in the vertical zones (11 to 1 o'clock and 5 to 7 o'clock) compared with the horizontal sectors (2 to 4 o'clock and 8 to 10 o'clock (Fig. 6). There were no significant relationships between ALD change by quadrant, upper/lower ONH, or by mapping ONH zones to Garway-Heath field mapping zones (Table 2).

To examine further the relationship between ALD change and NFL thickness, we divided the subjects into the three groups described above (Table 1). The change in ALD with IOP change was categorized into those with shallower ALD (negative change), those that did not move significantly, and those with deeper ALD (positive change). In this analysis, for each subject, the ALD change in a clock hour region was compared with the NFL thickness in that clock hour for that patient. A model divided the regional data in to tertiles, and for each regional group (those moving in a negative direction, those judged not to have moved, and those moving in a positive direction), the association between ALD change and NFL thickness was assessed. For regions with ALD change in a positive direction, that is, those that were deeper at higher IOP compared with lower IOP, the local regions that had corresponding greater NFL thickness had significantly greater change in ALD ($P < 0.0001$; Table 3).

The mean change in ALD by quadrant was greater in the inferior and and superior optic nerve head, compared with nasally and temporally, but was not significant ($P = 0.2$; Supplementary Table S2). The models that compared mean ALD and mean change in ALD to the NFL thickness in each quadrant of the disc also found no significant associations (Supplementary Table S2). The mean ALD and mean change in ALD were not significantly different by clock hour of the nerve head when the data were not paired to match each subject with its own NFL thickness (Supplementary Table S3).

Optic Nerve Head Diameter Change

The mean diameter of the ONH at BM opening, as well as the diameter difference at each clock hour, was compared at each IOP difference pairing. For all 42 pairs of IOP comparisons, the mean diameter change at higher compared with lower IOP was only 0.014 ± 0.066 mm (difference from zero not significant, $P = 0.18$). Models that compared the degree of IOP change to change in disc diameter or area for the overall disc or the six regional comparisons did not find any significant relationship (Supplementary Table S4).

Discussion

We found that baseline ALD was highly correlated to cup/disc ratio, rim width, and cup volume, but not to parameters estimating the number of RGC axons in the ONH (NFL thickness and visual field indexes). The depth of the lamina varies among eyes at baseline and remodels during the glaucoma process. The baseline, clinical disc parameters, such as cup/disc ratio, are determined by the amount of neuro-glial tissue in the anterior ONH and the position and shape of the connective tissue of the more posterior lamina cribrosa. Thus, increasing cup/disc ratio or cup volume would occur from both loss of RGCs and from posterior migration of the lamina. Field loss would be associated with neuro-glial atrophy, but would only be indirectly related to the remodeling attendant to glaucoma. Thus, the ALD at a single point in time and at a particular IOP is a result of its original position (interindividual variability) and the connective tissue alterations caused by glaucoma. Based our data, as well as prior reports, ALD is more closely related to the clinical appearance of the disc than to the severity of functional loss at a given point in time. This suggests

Table 2. ALD Change Association With Glaucoma Damage by Region Within Each Disc

Region	Variable	*N*	Change in ALD (μm) Regression Coefficient (95% CI)	*P* Value
Clock hour (12)	NFL thickness, μm	494	1.70 (0.72, 2.67)	0.0007
Quadrant (4)	NFL thickness, μm	168	1.00 (−0.59, 2.60)	0.22
Disc to field map zones (6)	Visual field score	242	−3.06 (−10.24, 4.13)	0.40
Upper/lower (2)	Visual field score	84	1.27 (−8.11, 10.66)	0.79

CI, confidence interval.

Table 3. Mean ALD Change Related to NFL Thickness in Three Subject Groups

Direction of ALD Change	*N*	Linear Regression Coefficient for NFL Thickness, µm	
		Estimate (95% CI)	*P* Value
−192 to −68 µm	132	1.00 (−0.81, 2.81)	0.28
−55 to 49 µm	158	1.31 (−0.21, 2.82)	0.09
52 to 384 µm	204	2.99 (1.47, 4.51)	0.0001

N, number of clock hour data points matchcing ALD change and NFL thickness.

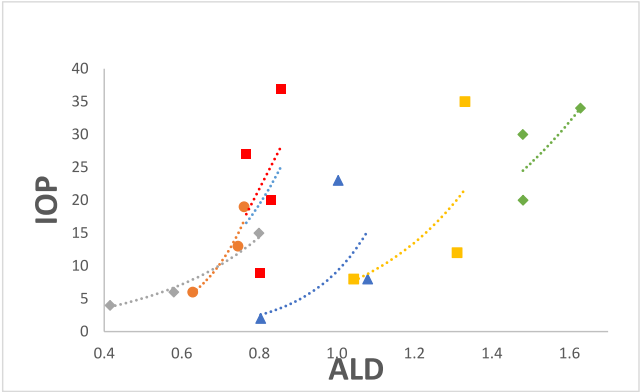


Figure 7. ALD for six subjects with images at three different IOP levels, with individual regression lines in color matching subject's three or four ALD value markers. Tendency for ALD change to be less at a higher range of IOP is evident, and in some subjects, the ALD change with IOP change was small.

that a single measure of ALD is unlikely to be the most useful biomarker for susceptibility to glaucoma damage.

We observed a variety of ALD behaviors when the IOP decreased in our subjects. After IOP lowering, ALD was often shallower, but sometimes was immobile, or even moved in the direction out of the eye. Although anterior (negative as defined here) ALD position at higher IOP seems counterintuitive, it could occur from the combined behavior of the peripapillary sclera and lamina, responding as a unit to IOP change under certain conditions of stiffness for both tissues. Consider that there are two main forces acting on the lamina: the translaminar pressure difference (IOP minus optic nerve tissue pressure) and stress generated circumferentially by IOP acting on the ONH through the sclera. Depending on how these two stresses act, the lamina could move either into or out of the eye with IOP decrease. Although the interaction between the peripapillary sclera and the lamina is complex, and the actual properties of their combined behaviors are not fully understood, some general, although simplified, statements may illustrate possible scenarios. One combination of idealized features would be low peripapillary scleral strain and high lamina strain, which would be expected to lead to lamina movement out of the eye as IOP changed from lower to higher. Another simplified example would be high scleral strain and low laminar strain, in which the lamina might move toward the vitreous as IOP became higher. Past reports have found that mean change in ALD is either positive (posterior) or negligible at higher IOP. Agoumi et al.[77] measured ALD change after acute IOP elevation by ophthalmodynamometry, detecting only 10 µm or less change in either direction. We did not identify past reports that documented negative directional movement of the magnitude observed here. It may be that investigators who reported no change in ALD[77,78] with IOP increase averaged the positive and negative movements among eyes, with a mean effect of no change. Indeed, in our own data, the net movement (mean of all eyes) was not statistically greater than zero. When, however, we converted ALD change to its absolute value, significant mean movement of the group of eyes was detected. Lee et al. reported that mean ALD in their patients declined with IOP reduction, but 41% of eyes had no reduction in depth and some moved in the opposite direction (anteriorly).[78] In their data, no eyes appeared to have exceeded the limit of intersession variability when moving anteriorly compared with our series in which a number of eyes did so. The intersession variation of 23 µm in their group and our data were very similar, although the eyes in their research were studied 3 months after IOP change, whereas the majority of our observations were separated by less than 1 month.

We found a strong association between the lower IOP level (in paired observations at two IOPs) and the amount of change in ALD—that is, there was more movement when the IOP was in a lower than a higher range. In fact, ALD change was more related to the level of IOP than to the magnitude of IOP change or the percent IOP change. This fits with the standard shape of stress–strain curves, which is an exponential relationship. When strain is low, a unit change in stress (IOP) induces greater strain change than when strains are already high. Thus, we would expect, and did in fact observe, more change from decreasing IOP by 10 mm Hg from 15 to 5 mm Hg than from 30 to 20 mm Hg. Observations of subjects who were measured at three IOP levels show this phenomenon (Fig. 7). For example, the report of Park et al.[79] found mean group changes of 20 to 30 µm from IOP lowering of 15 mm Hg, from a baseline of 38 mm Hg, whereas our ALD change values ranged up to 10 times greater with similar absolute lowering, but from a lower baseline IOP level. Thus, it is important to consider the range within which IOP is measured in assessing ALD change.

We found that the magnitude of IOP change was not significantly related to ALD change. However, some studies report greater change in mean ALD with greater percent IOP lowering, as well as with baseline ALD, male sex, angle closure glaucoma, and worse visual field damage level.[78–81] The magnitude of mean ALD change reported by Reis et al.[82] varied from 1 µm at 1 week after surgery to 17.9 µm at 6 months. These values are dramatically less than those reported here and elsewhere. Our mean ALD alteration represented a 10% change in eyes with 20% IOP lowering as in another study.[78] Note that such generalizations fail to account for the several variables affecting ALD change. Reis et al.[82] found, as we did, that ALD was not statistically related to change in IOP. If IOP change were calculated as a percentage, the IOP base level becomes part of the equation, and the data may actually be indicating, as described above, that the operative variable affecting ALD change is really the IOP level. For example, if IOP decreases by 5 mm Hg from either 20 or 10 mm Hg, the former is 25% lower, whereas the latter is a 50% decrease. In this way, the apparently greater effect (of the same IOP decrease in mm Hg) is actually due to the lower base IOP.

The mean ALD change with IOP change may depend on the severity of glaucoma damage, as found in studies cited above and suggested by our data. The trend was for eyes with advanced damage to have less ALD change with IOP change. This is what would be expected if the remodeling effect of glaucoma produced a stiffer lamina. Likewise, we saw greater ALD movement in eyes with only modest glaucoma visual field damage. The most definitive evidence for greater stiffness

in areas of greater glaucoma damage was seen in our models that compared regional change by clock hour within each ONH to the NFL thickness entering that clock hour. Although the mean ALD change in a quadrant or clock hour across all subjects was not statistically significant, the regional ALD change within an eye was significantly less with thinner NFL—suggesting that the more damaged areas were stiffer. We do not know if these areas were stiffer at baseline or became so after NFL atrophy. This association is obscured if one looks only at the overall mean ALD change (even at the level of clock hour) because that statistic averages all eyes with their variable degrees of damage. Internal regional comparisons within glaucoma eyes will better denote susceptibility or mechanical behavior with respect to the stage of damage. Cross-sectional data cannot distinguish whether the greater stiffness in more damaged areas was present at baseline and is causative or occurred as a result of remodeling during the injury process. Longitudinal studies are needed to distinguish between these possibilities.

ALD change as measured in clinical research may also depend on the interval between IOP change and imaging. The present data included assessment of ALD change that was measured at different intervals, many less than 1 month apart. Other reports have used a variety of intervals between measurements, from those using acute effects with ocular compression for minutes to studies evaluating depth change years after altering IOP by trabeculectomy. When IOP was acutely raised by ocular compression, no mean change in ALD was measured.[76] Another study[79] found a greater change in ALD at 1 week postoperatively than after 1 month, although the differences were modest. Lee et al. found minimal differences in ALD change between 6 months and 2 years after surgery.[83] We should keep in mind that the shorter the interimage interval, the more the effect (if any) is an immediate, biomechanical response, whereas studies over longer intervals include the effect of chronic remodeling and IOP variation during the interimage period.

To calculate mean ALD, we fitted the data for each scan to a sixth-order polynomial, with mean r^2 values of 0.95 and an average of 146 marked locations per ONH. In most other investigations, ALD was judged by a single point (the "maximum depth") or by three points selected in each of 10 single scans. Such limited approaches cannot detect regional changes nor can they characterize the behavior of a structure with a complicated shape. Thakku et al.[84] used swept-source OCT to generate a shape index for the anterior lamina constructed from modeling of a large number of points.[84] Using this method, changes in the shape of the lamina can be estimated as an overall index.[76] However, this approach cannot compare local regions of the lamina to others, as it reduces the structure to a single parameter. Although use of the actual marked locations may seem advantageous, it would preclude ideal comparisons between image sessions, because it is not possible to assure that the same points were measured in each set. Due to shadowing of overlying vessels, we could mark approximately 75% of the scan area. Reis et al.[82] reported that they could mark 47% of the anterior laminar area.

The reference location for measurements of ALD is BM opening. We did not find a significant increase in the diameter or area of BM opening with increase in IOP. Although increases in the diameter of the ONH posterior to BM were seen in experimental glaucoma in monkeys[85] and in human glaucoma,[86] the area of BM opening itself is stable over time[87] and has been found to change <1% with IOP decrease after surgery.[79,83] Although BM would move along with the retina and choroid as axial length changes with IOP change, there is no reason to consider that the diameter of BM opening would be altered by modest changes in IOP. This is reassuring, as some software now uses BM opening as the reference position for ONH analysis programs in clinical management.[72] Although the neural canal at the ONH widens dramatically behind BM in glaucoma, the scleral border defining that canal is not yet resolved sufficiently by OCT to measure this canal expansion.

Our study had some limitations. Patients had recently undergone either a surgical or laser procedure and may not be representative of all those with open angle glaucoma; however, the range of damage represented by our subjects included mild, moderate, and severely damaged eyes. It is sometimes difficult to mark the anterior lamina position where there is a change in contrast between the prelaminar ONH with no connective tissue and the anterior lamina cribrosa with its collagen and elastin. To our knowledge, no software has automated this process and been validated. Furthermore, the view of the lamina is blocked in some areas by the shadowing effect of overlying retinal blood vessels. This reduced our ability to mark approximately 25% of the lamina. Although this is not ideal, it is clearly a step forward over selecting one or three points along the lamina border as performed in many early studies.

In summary, we measured baseline values and changes in the ONH with changes in IOP. The ALD was highly correlated to separate measures of ONH features, such as cup/disc ratio, cup volume, and rim width. Dynamic change in ALD was greater at lower IOP than at higher IOP, as would be expected from a typical mechanical stress–strain relationship. There were trends suggesting that ALD becomes less mobile with greater glaucoma damage. Movement of the anterior lamina cribrosa with IOP change could represent a prognostic marker in glaucoma. To achieve this goal, longitudinal studies are needed, along with improved OCT resolution and automation of tissue position software.[88]

Acknowledgments

The authors thank Jessica Shackelford for excellent technical assistance in this project.

Disclosure: **H. Quigley**, None; **K. Arora**, None; **S. Idrees**, None; **F. Solano**, None; **S. Bedrood**, None; **C. Lee**, None; **J. Jefferys**, None; **T.D. Nguyen**, None

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