# Lamina depth and thickness correlate with glaucoma severity

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**Purpose:** To evaluate the correlation between lamina cribrosa (LC) morphology and glaucoma severity in patients with primary forms of open-angle glaucoma (OAG) using enhanced depth imaging spectral-domain optical coherence tomography (SD-OCT) and Humphrey visual field test (HVF). **Subjects and Methods:** Patients with OAG ($n = 166$), divided into normal-tension glaucoma (NTG) and high-tension glaucoma (HTG) groups ($n = 66$ and $n = 100$), were imaged using SD-OCT to obtain horizontal B-scan images of the optic nerve head (ONH). Laminar depth (LD) and laminar thickness (LT) were measured at the center of ONH. **Results:** The mean (±standard deviation) values of LD, LT, and visual field mean deviation (MD) were $555.4 \pm 142.3$ μm, $179.9 \pm 49.7$ μm, and $-5.7 \pm 6.4$ dB, respectively. In the multivariate linear regression analysis, LD, LT, and intraocular pressure (IOP) were significantly correlated with MD ($P = 0.007$, $P = 0.037$, and $P = 0.004$, respectively). In the subgroup analyses, only LD was associated with MD in the NTG group ($n = 66$), whereas LT and IOP were correlated with MD in the HTG group ($n = 100$). Neither axial length nor central corneal thickness was associated with LD or LT. **Conclusions:** Glaucoma severity, as measured by HVF MD, shows significant correlations with LD and LT, with greater severity associated with increasing LD and decreasing LT. Normal- and high-tension OAG patients have different associations with LD and LT, which implies that the pathogenesis of these two entities might be different.

**Key words:** Glaucoma, lamina cribrosa, optic nerve, optical coherence tomography

Primary forms of open-angle glaucoma (OAG) are characterized by a progressive optic neuropathy with typical optic nerve head (ONH) damage or glaucomatous visual field (VF) defects.[1] The lamina cribrosa (LC), a multi-layered sieve-like structure in the ONH, has been proposed as a primary site of axonal damage in glaucoma.[2] However, in the past, quantitative evaluation of LC tissue *in vivo* was not possible due to the presence of prelaminar neuroretinal tissue.

Improvements in technology have enabled optical coherence tomography (OCT) to provide high-resolution cross-sectional images of the ONH *in vivo*.[3] Furthermore, enhanced depth imaging (EDI) using spectral-domain (SD) OCT enables visualization of the LC *in vivo*.[4-12] Using this imaging method, studies on OAG have been performed to investigate the structure-function relationship between the morphology of LC and glaucoma severity.[5,12,13] Inoue *et al*.[5] showed a significant positive correlation between laminar thickness (LT) and retinal sensitivity in glaucoma by linear regression analysis. Park *et al*.[12] also reported a logarithmic correlation between LT and retinal sensitivity in OAG patients. Recently, Ren *et al*.[13] revealed that the anterior LC surface depth increased with worse VF status in younger eyes with high-risk ocular hypertension and early glaucoma. We investigated the correlation between LC morphology, including both LT and laminar depth (LD), and glaucoma severity using EDI SD-OCT and Humphrey VF (HVF) testing in OAG patients.

## Subjects and Methods

The study was performed with the informed consent of the participants and followed the Declaration of Helsinki and was approved by the Institutional Review Board.

All patients were recruited prospectively from December 2011 to October 2012 from the glaucoma clinics. Subjects were recruited consecutively based on the availability of study personnel. All subjects received comprehensive ophthalmic examinations that included best-corrected visual acuity, Goldmann applanation tonometry, slit-lamp biomicroscopy, central corneal thickness measurement (PachPen, Accutome, Malvern, PA, USA), and axial length measurement (IOL Master, Carl Zeiss, Meditec Inc., Dublin CA, USA). All subjects also underwent VF testing using 24-2 Swedish Interactive Threshold Algorithm – Standard algorithm (Humphrey Field Analyzer; Carl Zeiss Meditec. Inc., Dublin, CA, USA) and ONH imaging by SD-OCT (Spectralis OCT, Heidelberg Engineering, Vista, CA, USA) within 6 months of the ophthalmic examination.

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For inclusion in this study, eyes with OAG were required to have a best-corrected visual acuity of ≥20/40 with axial length <30 mm, presence of a normal anterior chamber and open-angle on slit lamp and gonioscopic examinations, a clear cornea, and not more than moderate cataract. Subjects with any other ophthalmic or neurologic condition that could result in VF defects were excluded from the study as they were those with a history of any refractive corneal surgery or intraocular surgery, except noncomplicated cataract surgery. When both eyes were eligible, one eye was randomly selected.

We defined OAG as having an open angle on gonioscopy and glaucomatous optic nerve damage (i.e., the presence of typical thinning of the neuroretinal rim or notching). Most patients also had an abnormal VF consistent with glaucoma. A glaucomatous VF change was defined as (1) outside normal limits on the Glaucoma Hemifield Test; (2) 3 abnormal points with $P < 5\%$ probability of being normal, 1 with $P < 1\%$ by pattern deviation; or (3) a pattern standard deviation of <5% as confirmed on two consecutive tests. The VF tests required a false-positive rate, false-negative rate, and fixation loss rate of <25%. Patients with historical untreated and treated intraocular pressure (IOP) ≤21 mmHg were classified as normal-tension glaucoma (NTG) while those with historical untreated or treated IOP >21 mmHg at least one measurement were classified as high-tension glaucoma (HTG). All patients diagnosed as NTG and HTG were treated with antiglaucoma medications when they enrolled in the present study.

Spectral-domain OCT of the ONH with EDI was obtained using the Heidelberg Spectralis OCT (Heidelberg Engineering, Vista, CA, USA). The methods have been described elsewhere in detail.[8,12,14,15] In our study, 6 radial B-scans of the ONH centered at the center of the disc were produced in the EDI mode. Among these B-scans, the horizontal frame that passed through the center of ONH was selected. Only good-quality scans (i.e., quality score ≥16) were used for analysis. The IOP measured by Goldmann applanation tonometry on the same day that the patient underwent the OCT examination was recorded.

The anterior depth of the LC (laminar depth [LD]) was determined as the distance between the reference plane and the anterior LC surface at the center of ONH. The reference plane was defined as the line connecting the 2 termination points of Bruch's membrane on each B-scan. When the termination of Bruch's membrane was not clear or the insertion was oblique, the extrapolated extension of the line along with the Bruch's membrane surface was used as the reference plane [Fig. 1]. If the ONH was tilted by myopic change, the deepest point on the horizontal plane was chosen for the measurement. The thickness of the LC (laminar thickness [LT]) was also measured on horizontal B-scan images. The LT was determined as the distance from the anterior LC surface to the posterior LC surface at the center of ONH. All measurements were performed using the software which was provided from Heidelberg SD-OCT. Interobserver reliability (as assessed by intraclass correlation coefficient [ICC]) was measured for LD and LT using two independent observers (MK, KDB) for a subset of the subjects.

Comparisons between NTG and HTG groups were performed using the independent *t*-test for continuous variables or Chi-square test for categorical variables. The relationships between the laminar morphology (LD and LT) and VF mean deviation (MD) were evaluated by linear regression analyses.
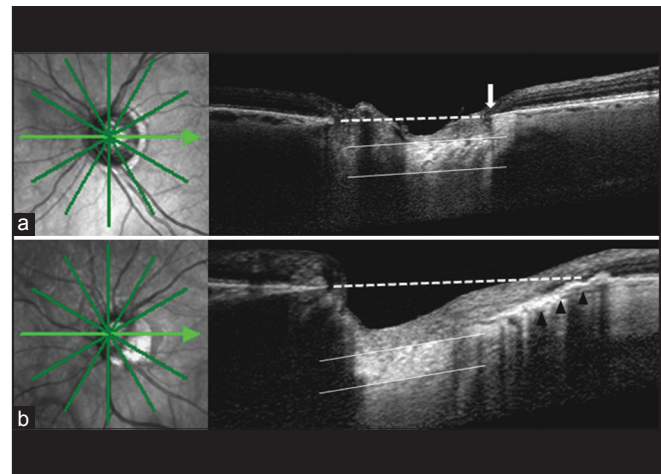


**Figure 1:** Representative reference planes (white-dotted lines) and lamina cribrosa (white lines). Infrared images (left column) show the radial section where the horizontal cross-sectional B-scans (right column) were acquired. (a) Example of the reference plane (white-dotted line) with clear Bruch's membrane termination (white arrow). (b) Example of unclear Bruch's membrane termination with border tissue (black arrowheads). The imaginary extension of the line along with the Bruch's membrane surface is used as reference plane (white-dotted line)

The HVF MD was treated as the dependent variable and other variables including laminar parameters (LD and LT) as the independent variables in all regression analysis assessing the structure-function relationship. Variables with $P < 0.2$ in the univariate regression analysis were entered in each multivariate regression analysis. Statistical analyses were performed using SPSS Statistics software (version 17.0, SPSS Inc., Chicago, IL, USA). The level of statistical significance was set at $P < 0.05$.

## Results

One hundred sixty-six patients were enrolled in the study. The subject characteristics are summarized in Table 1. Of the 166 patients, 66 patients had NTG and 100 patients had HTG. All parameters except IOP were not significantly different between NTG and HTG group. Ten patients were excluded due to poor EDI scan quality from this study.

The interobserver reliability for LC measurements, determined using a randomly selected subgroup of sixty patients, was excellent (ICC = 0.972 and 0.779 for LD and LT, respectively) as judged by Fleiss criteria.[16]

The univariate regression analysis including all OAG patients showed that the LC parameters (LT and LD) and the IOP are significantly associated with the MD value [Table 2]. These variables remained significant after multivariate regression analysis (adjusted $R^2$ = 0.096; $P$ = 0.007, $P$ = 0.037, and $P$ = 0.004, respectively).

In the subgroup analysis of only NTG patients, the LD was associated with the MD both in univariate and multivariate analysis, whereas the LT and the IOP were not significantly associated with the MD [Table 3]. When only HTG patients were included, the LT and the IOP were significantly associated with the MD in univariate and multivariate analysis, but the LD was not associated with the MD [Table 4].

### Table 1: Baseline characteristics of subjects

| | OAG (*n*=166) | NTG (*n*=66) | HTG (*n*=100) | *P* |
|---|---|---|---|---|
| Age (year) | 70.0±12.4 | 68.7±13.2 | 70.9±11.8 | 0.265* |
| Gender (% male) | 48.8 | 40.9 | 54.0 | 0.114† |
| Intraocular pressure (mmHg) | 13.6±3.1 (range 8-26) | 12.3±2.4 (range 8-20) | 14.5±3.3 (range 8-26) | <0.001* |
| Axial length (mm) | 24.7±1.5 (range 21.76-29.50) | 24.8±1.5 | 24.7±1.5 | 0.491* |
| Central corneal thickness (μm) | 538.8±39.0 (range 435-641) | 537.1±26.7 | 539.9±45.4 | 0.644* |
| MD (dB) | −5.7±6.4 (range −26.96-1.65) | −5.7±6.1 | −5.7±6.6 | 0.981* |
| LD (μm) | 555.4±142.3 (range 183-1047) | 539.4±140.5 | 565.9±143.2 | 0.241* |
| LT (μm) | 179.9±49.7 (range 82-316) | 177.7±53.0 | 181.4±47.6 | 0.635* |

*Comparison between NTG and HTG by student t test. †Comparison between NTG and HTG by Chi-square test. OAG: Open-angle glaucoma, NTG: Normal-tension glaucoma, HTG: High-tension glaucoma, MD: Mean deviation, LD: Laminar depth, LT: Laminar thickness

### Table 2: Univariate and multivariate regression analyses of visual field mean deviation in all patients (*n*=166)

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | Regression coefficient | 95% CI | *P* | Regression coefficient | 95% CI | *P* |
| Gender | −0.671 | −2.632-1.296 | 0.503 | | | |
| OAG type | −0.002 | −2.033-1.985 | 0.981 | | | |
| Axial length | 0.001 | −0.651-0.658 | 0.992 | | | |
| CCT | 0.098 | −0.009-0.041 | 0.208 | | | |
| LD | −0.186 | −0.015--0.002 | 0.016 | −0.208 | −0.016--0.003 | 0.007 |
| LT | 0.191 | 0.005-0.044 | 0.014 | 0.157 | 0.001-0.039 | 0.037 |
| IOP | 0.198 | 0.095-0.710 | 0.011 | 0.221 | 0.147-0.752 | 0.004 |

OAG: Open-angle glaucoma, CI: Confidence interval, CCT: Central corneal thickness, LD: Laminar depth, LT: Laminar thickness

### Table 3: Univariate and multivariate regression analyses of visual field mean deviation in normal-tension glaucoma patients (*n*=66)

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | Regression coefficient | 95% CI | *P* | Regression coefficient | 95% CI | *P* |
| Gender | 0.071 | −2.210-3.956 | 0.574 | | | |
| Axial length | 0.111 | −0.550-1.439 | 0.375 | | | |
| CCT | 0.006 | −0.056-0.059 | 0.960 | | | |
| LD | −0.254 | −0.022-0.000 | 0.039 | −0.204 | −0.022-0.000 | 0.045 |
| LT | 0.165 | −0.009-0.048 | 0.185 | 0.079 | −0.020-0.038 | 0.315 |
| IOP | 0.161 | −0.218-1.043 | 0.196 | 0.169 | −0.200-1.065 | 0.177 |

CI: Confidence interval, CCT: Central corneal thickness, LD: Laminar depth, LT: Laminar thickness

### Table 4: Univariate and multivariate regression analyses of visual field mean deviation in high-tension glaucoma patients (*n*=100)

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | Regression coefficient | 95% CI | *P* | Regression coefficient | 95% CI | *P* |
| Gender | −0.127 | −4.289-0.947 | 0.208 | | | |
| Axial length | −0.068 | −1.183-0.582 | 0.501 | | | |
| CCT | 0.134 | −0.009-0.048 | 0.183 | 0.089 | −0.016-0.042 | 0.383 |
| LD | −0.147 | −0.016-0.002 | 0.145 | −0.172 | −0.017-0.001 | 0.082 |
| LT | 0.210 | 0.002-0.056 | 0.036 | 0.227 | 0.005-0.058 | 0.021 |
| IOP | 0.236 | 0.083-0.866 | 0.018 | 0.244 | 0.088-0.892 | 0.017 |

CI: Confidence interval, CCT: Central corneal thickness, LD: Laminar depth, LT: Laminar thickness

# Discussion

We found a small but significant correlation between glaucoma severity as measured by VF MD and LC parameters such as LT and LD *in vivo* using EDI SD-OCT. As glaucoma severity worsened, the LT was thinned and the LD was deepened in OAG patients. The level of IOP in these treated patients who had not undergone incisional glaucoma surgery was also associated with MD. In the subgroup analysis, the LT and IOP were significantly correlated with MD in the HTG group, whereas only the LD was significantly correlated with MD in the NTG group.

The concept of structure-function relationship in glaucoma patients is important for both grading the severity of disease and understanding the natural history of the condition.[17] Since the LC is considered to be an important site of axonal injury in glaucoma, many researchers have made efforts to visualize the LC and analyze the structure-function relationship between the LC and glaucoma severity.[5,12,18] There are cumulative data demonstrating the linear[5] or logarithmic[12] correlation between the LT and glaucoma severity. Consistent with previous studies, we found a significant correlation between the LT and the VF MD using linear regression analysis. Our results show that a structure-function relationship exists between LC measurements and functional loss in glaucoma, which could be important for understanding the pathophysiology of glaucoma, and potentially predicting its course.

Because glaucomatous ONH cupping is a common clinical feature of glaucoma and is a combination of two components – prelaminar and laminar cupping, it is unsurprising that the LD is deeper as the severity of glaucoma damage increases. Several postmortem studies in nonhuman primate experimental glaucoma have been described the posterior deformation[19-21] and outward migration[22] of LC in response to a chronic IOP elevation. However, before the EDI technique using SD-OCT was developed, quantitatively analyzing the LD *in vivo* was not possible. With the advent of technical improvements that allow EDI, several studies have examined LD change with human eyes *in vivo* after glaucoma surgery or IOP changes.[23-26] Recently, studies have been performed focusing on the direct relationship between the LD and glaucoma. Furlanetto *et al*.[23] demonstrated that the central and mid-peripheral LC were located more posteriorly in glaucomatous eyes and eyes with VF defects as compared to normal eyes and fellow eyes with no VF defects. Ren *et al*.[13] reported the relation between the anterior LC surface depth and MD in early glaucoma (VF loss less severe than − 6 dB [MD]) or ocular hypertension patients. In their study, the LD increased with worse VF status in younger eyes but not in older eyes. In the present study, our data also showed a significant negative correlation between the LD and the MD.

In addition, our results showed that the association between the LC and glaucoma severity was different depending on the type of glaucoma and the association of IOP with glaucoma severity also differed with the type of glaucoma. Within the NTG group, the LD was significantly correlated with the MD, whereas the LT and the IOP were not. In contrast, the LT and the IOP were significantly correlated with the MD within the HTG group, but LD was not significantly correlated with the MD. These results could be explained in several ways. First, the pathogenesis of glaucomatous damage could differ between the NTG and the HTG group. Although the pathogenesis of OAG is still unclear, an elevated IOP is the single most important risk factor for the development or progression of glaucomatous optic neuropathy in HTG patients.[27-29] In contrast, there is evidence that in addition to IOP level and/or fluctuation, ocular and systemic vascular abnormalities affect the development and progression of NTG.[30-32] Recently, Killer *et al*.[33] demonstrated an impaired circulation of cerebrospinal fluid (CSF) in NTG patients using computed tomography cisternography of the brain. The impairment of CSF circulation in these NTG patients could result in reduced neurotoxin clearance along the optic nerve.[34] The high IOP in HTG may cause compressive change of LC while low CSF pressure in the subarachnoid space surrounding the LC may result in deepening of LC in NTG due to lack of structural or metabolic support. Thus, worsening disease in NTG could cause relatively more LC deepening than thinning. In contrast, the LC of HTG could be thinned as the disease progresses. If a relationship between LC change and glaucoma progression is established, clinicians could potentially use this relationship to evaluate the disease state and the risk of progression.

Second, the structural properties of the LC might be different in the NTG patients and the HTG patients. Park *et al*.[12] demonstrated that the LT in the NTG group was significantly thinner from the early and mid-stages of glaucoma than that in the HTG group. With this result, the authors suggested that the thinner LC of the NTG group might have contributed to the development of retinal ganglion cell damage in a normal IOP range. We found the LT of the NTG group was not significantly thinner than that of the HTG group in the present study. Population differences, including the relatively long axial length of patients in the present study and differences in patient characteristics, including race, could be explanations for the discrepancy between our study and Park *et al*. Further longitudinal study is needed to determine the cause-effect relationship between glaucoma and LC morphology.

Several limitations must be acknowledged in this study. The precision of the relationship model was relatively low; in our model, the $R^2$ for all OAG patients was 0.096 and the $R^2$ for subgroup analysis models was 0.106 for HTG group and 0.061 for NTG group, which indicates that the explanatory power of these models is weak. Considering that glaucoma is a multifactorial disease with genetic and environmental components and the relatively poor agreement of optic disc structural changes with functional changes in glaucoma,[35] it seems unsurprising that these values were not stronger. In addition, the methods for measuring the depth and the thickness of the LC *in vivo* must be validated, especially for eyes with myopic tilted disc for which the configuration of LC may be different; this could influence the variability of measurements. However, in the present study, only five eyes showed a tilted disc configuration probably because most of the population of this study was Caucasian (69.3%). Thus, possible variability of measurement from myopic tilted disc could be minimized in this study. Furthermore, because of the cross-sectional nature of this study, it is not possible to determine the cause-effect relationship between the LC configuration and the glaucoma severity. Further prospective, longitudinal study is warranted.

## Conclusions

We measured LC parameters including the LT and LD *in vivo* using EDI SD-OCT and demonstrated a significant correlation between the LC parameters and the VF MD in OAG patients. Our results show a structure-function relationship between the LC and peripheral visual sensitivity. In addition, our results suggest that the LC may be different or act differently according to the OAG subtype, NTG versus HTG. Further research in this area is warranted to confirm these findings.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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