Lamina Cribrosa Configuration in Tilted Optic Discs With Different Tilt Axes: A New Hypothesis Regarding Optic Disc Tilt and Torsion

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Purpose. To determine the configuration of the anterior lamina cribrosa (LC) surface in eyes with different tilt axes.

Methods. A total of 114 eyes (66 glaucomatous eyes and 48 healthy eyes) with tilted optic discs (ovality index > 1.5) were divided into vertical- and horizontal-tilt groups according to their optic disc tilt axis. Serial horizontal B-scan images of the ONH were obtained from each eye using enhanced-depth imaging spectral-domain optical coherence tomography. After three-dimensional reconstruction of the images, the anterior LC surface depth (LCD) was measured in each of the oblique scans containing the long disc axis and in the seven horizontal B-scans that divided the anterior LC surface vertically into eight parts.

Results. The configuration of the anterior LC surface along the long disc axis differed markedly between groups. The vertical-tilt group had a larger LCD at superior locations than at inferior locations, while the pattern was the opposite in the horizontal-tilt group. The RNFL thinning in glaucomatous eyes was most prominent at both the superotemporal and inferotemporal sectors in the vertical-tilt group, while it was predominated at the inferotemporal sector in the horizontal-tilt group.

Conclusions. The configuration of the anterior LC surface in eyes with tilted optic disc tilt axis suggested that the horizontally-tilted optic discs may not be resulted from the optic disc rotation, but from the optic disc tilt centered on the oblique axis. The preferential location of RNFL thinning could be explained by the LCD profile differing according to the tilt axis.

Keywords: tilted disc, torsion, lamina cribrosa, spectral-domain optical coherence tomography, myopia

Myopia has been acknowledged as one of the risk factors for open-angle glaucoma (OAG).1–4 but the mechanism underlying glaucomatous damage in myopia remains unclear. An increasing body of literature suggests that optic disc tilt may give a clue to understanding glaucomatous damage in myopic eyes.5–8 Optic disc tilt is a common condition in myopic eyes, and is associated with oblique insertion of the optic nerve into the globe.9 Based on the anatomy of tilted optic discs and their relationship with the degree of myopia,10–12 it is believed that this condition is caused by axial elongation of the globe.13,14 Since the axial elongation is centered mostly on the posterior pole, the temporal optic disc margin can be stretched and tilted temporally on the vertical axis, resulting in a vertically oval optic disc.12,13 This process may stretch the optic nerve fibers in the temporal direction, leading to damage of axons.15–18 The risk of OAG is reportedly greater in eyes with a vertically tilted optic disc, and that the degree of tilt is positively associated with the severity of visual-field damage.5,9,11,12,15

In certain cases, the elliptical optic discs are oblique or even horizontally oval. This is frequently termed “torsion,” because such optic discs may appear to be rotated about the z-axis traversing the eye in an anterior-posterior direction.9 As with disc tilt, this optic disc “torsion” has been associated with glaucoma. It has been reported that the degree of optic disc rotation, as defined by the deviation of long disc axis from the vertical axis, is correlated with visual-field sensitivity,8 and that the direction of the optic disc rotation is correlated with the location of the visual-field defect.5 It has been suggested that the rotation of the optic disc may twist the axonal fibers and thereby impose an additional stress upon them.5,8 However, the notion of optic disc rotation is merely a presumption that is based on the shape of the optic disc and the orientation of the retinal vessels.9 Moreover, the mechanism underlying glaucomatous optic nerve damage in the rotation of the optic disc is not yet fully understood.

The lamina cribrosa (LC) has been a key focus in the investigation of glaucoma pathogenesis.19–23 It has been suggested that increased stress and strain within the LC that are induced by IOP elevation may compromise axoplasmic transport by various mechanisms.24,25 We hypothesized that the LC can be deformed during optic disc tilt (or rotation), thereby provoking glaucomatous axonal damage. If this is true, investigation of LC characteristics in eyes with different optic disc tilt axes may provide clues about the relationship between myopic optic disc tilt and glaucomatous optic nerve damage.

The aim of this study was to determine whether the link between glaucoma and myopic optic disc tilt can be clarified by investigating the LC configuration in tilted optic discs. To this
end, we measured the profiles of the anterior LC surface depth (LCD) in tilted optic discs with different tilt axes and investigated the relationship between LCD and glaucomatous retinal nerve fiber layer (RNFL) thinning.

**METHODS**

**Participants**

This investigation was based on the database of OAG patients and healthy subjects included in the Lamina Cribrosa Exploration Study (LCES) and the Investigating Glaucoma Progression Study (IGPS), which are ongoing prospective studies at the Seoul National University Bundang Hospital Glaucoma Clinic (Seongnam, Korea). Written informed consent to participate was obtained from all subjects, and the study protocol was approved by the Seoul National University Bundang Hospital institutional review board and followed the tenets of the Declaration of Helsinki.

The medical records of OAG patients and healthy subjects who were enrolled in the LCES or IGPS between June 2010 and June 2014 were reviewed. All participants included in the two studies underwent comprehensive ophthalmic examinations that included assessment of visual acuity, Goldmann applanation tonometry, refraction tests, slit-lamp biomicroscopy, gonioscopy, and dilated stereoscopic examination of the optic disc. They also underwent central corneal thickness measurement (Orbscan II; Bausch & Lomb Surgical, Rochester, NY, USA), axial length (AL) measurement (IOL master version 5; Carl Zeiss Meditec, Dublin, CA, USA), corneal curvature measurement (KR-1800; Topcon, Tokyo, Japan), fundus photography and red-free fundus photography (EOS D60 digital camera; Canon, Utsunomiya, Japan), enhanced-depth imaging (EDI) spectral-domain optical coherence tomography (SD-OCT; Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany) scanning of the optic disc, circumpapillary RNFL thickness measurement, and standard automated perimetry ( Humphrey Field Analyzer II 750, 24-2, Swedish interactive threshold algorithm; Carl Zeiss Meditec).

To be included in the present study, eyes had to be myopic (spherical equivalent < -0.5 diopters [D]) and have tilted optic discs with an ovality index of greater than 1.3 (see the section entitled “Defining the Optic Disc Tilt and Determining the Axis and Direction of Optic Disc Tilt”) and tilted optic disc tilt, which might have occurred along the oblique reference than the foveal–disc axis because the former allows swelling of the optic disc. A normal visual field was defined as the absence of glaucomatous visual-field defects and neurologic field defects. The baseline IOP was defined as the mean of at least two measurements made within 4 weeks of each other.

The exclusion criteria were eyes with a visual acuity of less than 20/40, a spherical refraction of less than -12.0 D, and a cylinder correction of greater than 3.0 D, the presence of a posterior staphyloma (that may deform the contour of the eyeball and possibly affect the LCD measurements), any abnormalities that affected the circumpapillary scan ring where the SD-OCT RNFL thickness measurements were obtained, a history of ocular surgery other than cataract extraction, intraocular disease (e.g., diabetic retinopathy or retinal vein occlusion) or neurologic disease (e.g., pituitary tumor) that could cause visual-field loss, when a good-quality image (i.e., quality score >15) could not be obtained at more than five sections of EDI 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), and when the images did not allow clear delineation of the anterior LC border at the measurement points in more than two selected B-scans. Healthy control eyes and OAG eyes were matched in terms of age and AL.

**Defining the Optic Disc Tilt and Determining the Axis and Direction of Optic Disc Tilt**

Tilted optic discs were defined as those having an ovality index of greater than 1.3, as per the inclusion criteria (see the section entitled “Participants”), where the ovality index was defined as the ratio of the longest diameter to the shortest diameter of the optic disc (Fig. 1A). Hosseini et al. recently described a new method to measure the optic disc tilt angle using OCT images and presented a moderate correlation between the OCT-based tilt angle and ovality index. However, we did not use this method, because it does not have a validated criterion to define the presence of the optic disc tilt.

Eyes with optic disc tilt were further classified according to the tilt axis. It was postulated that the currently purported “torsion” of the optic disc would actually be another form of optic disc tilt, which might have occurred along the oblique axis, rather than as a result of optic disc rotation along the plane parallel to the retina. Thus, in the present study, the tilt axis was assessed rather than defining the optic disc “torsion.” The optic disc tilt axis was defined as the angular deviation of the long axis of the optic disc from the line perpendicular to the foveal–Bruch’s membrane opening (BMO) axis (Figs. 1B, 1C). The foveal–BMO axis is considered to be a more reliable reference than the foveal–disc axis because the former allows anatomically consistent regionalization among the eyes.

However, the fovea is not visible with EDI optic disc scanning, and the BMO cannot be determined with fundus photography. To overcome this limitation, the BMO was determined using the enface image of the SD-OCT data set (Fig. 1B), and the image was then superimposed on the fundus photograph (Fig. 1C). Two images were aligned using the blood vessels as the reference on ImageJ software (http://imagej.nih.gov/ij/; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA). The center of the BMO and the fovea were then connected and defined as the foveal–BMO axis. Only an acute angle was considered, regardless of the direction of deviation of the long axis from the reference line. Optic discs with an angle of less than or equal to 20° were categorized as having a vertical tilt (included in the vertical-tilt group), while those with an angle of greater than 20° were categorized as having a horizontal tilt (included in the horizontal-tilt group).

The direction of tilt was determined based on the tilt axis and the location of parapapillary atrophy (PPA). In more detail,
The BMO was demarcated on the enface image of the SD-OCT data set constructed using a maximum intensity projection (blue dotted line). The enface OCT image (B) was superimposed on the fundus photograph and rotated to adjust any misalignment between the images using the blood vessels as the reference. The center of the BMO and the fovea were then connected and defined as the foveal–BMO axis (green dashed line). The horizontal and vertical tilts were classified for each eye in both the healthy and OAG groups, which meant that there were four experimental groups: (1) healthy eyes with vertical tilt, (2) healthy eyes with horizontal tilt, (3) OAG eyes with vertical tilt, and (4) OAG eyes with horizontal tilt.

The ovality index and optic disc tilt axis were measured on fundus photographs using ImageJ software by two independent observers (KML and EJL) who were masked to subjects’ clinical information. Any discrepancy between observers in determining the presence of optic disc tilt or the classification of tilt axis was resolved by consensus.

**SD-OCT Measurement of the LCD**

The LCD was determined by measuring the distance from the BMO plane to the level of anterior LC surface. First, the configuration of the anterior LC surface was evaluated along the horizontal axis of the optic disc ellipse in each group, in order to verify the correspondence of the LCD profiles along those axes between the vertical- and horizontal-tilt disc groups. To do this, the OCT data volume was constructed in three dimensions using image-processing software (Amira 5.5.2; Visage Imaging, Berlin, Germany), and an oblique scan was generated using the Amira software along the long axis of the optic disc (the longest diameter of the optic disc, Fig. 2A). The LCD was then measured at five equidistant points in each scan dividing the anterior LC surface plane into six parts (Fig. 2B). The extent of the anterior LC surface was determined by the most visible end of the anterior LC surface. Each of the five LCD measurements obtained in the oblique image was termed as the LCD-LA (LCD-LA1 → LCD-LA5; superior LCD → inferior LCD in the vertical-tilt group, temporal LCD → nasal LCD in the horizontal-tilt group).

Seven horizontal B-scan images that divided the anterior LC surface into eight equal parts vertically were then selected from the OCT data set (Fig. 2A). In each selected B-scan, the distance from the reference line connecting the two termination points of Bruch’s membrane to the level of the anterior border of the LC was measured at three points: the maximally depressed points and two additional points (separated by 100 μm in both the nasal and temporal directions; Fig. 2C). Only temporal adjacent points were selected when the nasally adjacent point was not visible due to the shadow of the trunk of the central retinal vessel. The distance was measured on the line perpendicular to the reference line using the built-in three-dimensional (3D) measurement tool of the Amira software. The mean of the three measurements (from the three points) was defined as the LCD of each B-scan image. The mean of the LCD measurements obtained from each seven equidistant B-scans was defined as the mean LCD of the eye. The LCD profiles were investigated from the superior to the inferior ONH (LCD1 → LCD7) and compared between the groups. Measurements were performed by two independent observers (KML and EJL) who were blinded to the subjects’ clinical information.

**Data Analysis**

The interobserver agreement regarding determination of the presence of optic disc tilt and the classification of the tilt axis were assessed using kappa statistics. The strength of the
agreement was categorized as follows according to the method proposed by Landis and Koch: 0 = poor, 0 to 0.20 = slight, 0.21 to 0.40 = fair, 0.41 to 0.60 = moderate, 0.61 to 0.80 = substantial, and 0.81 to 1.00 = almost perfect. The interobserver reproducibility of LCD measurement was assessed by calculating the intraclass correlation coefficients (ICC (2, 1)). The generalized estimating equation regression model (GEE) was applied to show the differences in the LCD patterns according to the tilt groups. Between-groups comparisons were performed using the $\chi^2$ test for categorical variables, and independent-samples $t$-test or ANOVA with the Sidak post hoc test for continuous variables. All tests were two-sided except the $\chi^2$ test, and the cutoff for statistical significance was set at $P$ less than 0.05. The raw data for $t$-tests were subjected to the Bonferroni correction on the basis of the number of comparisons within each analysis. Considering the intraclass correlations of the LCD or RNFL thickness in different regions, the GEE analysis was also performed to compare the LCD-LA, LCD, and RNFL thickness between the groups. All statistical analyses were performed with commercially available software (Stata version 13.0; StataCorp, College Station, TX, USA).

### Results

Initially, 220 healthy subjects and 180 glaucoma patients with myopia were enrolled in the study. Optic disc tilt was found in 56 healthy eyes (25.5%) and 79 glaucomatous eyes (43.9%). After matching the OAG patients and healthy subjects for age and AL between groups, 53 healthy eyes and 73 glaucomatous eyes of 126 subjects remained, of which 9 were excluded because of poor scan image quality (more than 5 missing sections out of an average of 65 sections), and 3 were excluded because of nonvisibility of the deepest LC in more than 2 horizontal B-scans. The anterior LC surface was readily visible in most of the B-scans in the remaining 114 eyes (48 healthy eyes and 66 glaucomatous eyes).

Of the 114 subjects who were finally included, 23 healthy and 39 glaucomatous eyes were categorized according to their optic disc tilt axis and assigned to the vertical-tilt group, and 25 healthy eyes and 27 glaucomatous eyes were similarly assigned to the horizontal-tilt group. The direction of tilt was temporal in all eyes in the vertical-tilt group, and inferior in all eyes in the horizontal-tilt group. The strengths of the interobserver agreement for the determination of optic disc tilt and the categorization of the tilt-axis groups were both almost perfect ($k = 0.956$ and 0.964, respectively). The interobserver ICC (2, 1) for the measurement of LCD was 0.997 (95% confidence interval [CI], 0.984–0.999). The demographic data for the subjects in each group are given in Table 1.

The configuration of the anterior LC surface along the long optic disc axis (LCD-LA) was assessed in each group, which revealed a clear difference between the vertical- and horizontal-tilt groups (Fig. 3). The anterior LC surface of the eyes in the vertical-tilt groups exhibited a W-shaped pattern with a prominent central hump in both the healthy ($P < 0.001$ for the LCD-LA1 versus 2; $P = 0.004$ for the LCD-LA2 versus 3; $P = 0.013$ for the LCD-LA3 versus 4; $P = 0.069$ for the LCD-LA4 versus 5 by the GEE; Fig. 3A), and the OAG eyes ($P < 0.001$ for the LCD-LA1 versus 2; $P = 0.001$ for the LCD-LA2 versus 3; $P = 0.036$ for the LCD-LA3 versus 4; $P < 0.001$ for the LCD-LA4 versus 5 by the GEE; Fig. 3B). In contrast, the contour of the anterior LC in the horizontal-tilt groups was U-shaped and did not have a central elevation in either the healthy ($P = 0.005$ for the LCD-LA1 versus 3; $P = 0.002$ for the LCD-LA3 versus 5 by the GEE; Fig. 3A), or the OAG eyes ($P < 0.001$ for the LCD-LA1 versus 3 and the LCD-LA3 versus 5 by the GEE; Fig. 3B). The difference in the pattern of the LCD-LA between the vertical- and horizontal-tilt groups was significant both in the healthy ($P = 0.021$ by the GEE and OAG eyes ($P = 0.036$ by the GEE; Fig. 3). More specifically, the regional LCD-LA slopes from the LCD-LA1 to 4, and 5 were all significant between the groups with the healthy eyes ($P = 0.012, 0.005, 0.011, 0.011$ by GEE, respectively) and significant in all but one region for the OAG eyes ($P < 0.001$, <0.001, 0.012, 0.697 by GEE, respectively).

The LCD profiles along the vertical meridian from the superior to the inferior ONH of each group are shown in Figure 4 and Table 2. In the healthy eyes, both the vertical- and horizontal-tilt groups showed a W-shaped LC with a central hump (in the vertical-tilt group, $P = 0.001$ for the LCD2 versus 5; $P = 0.037$ for the LCD5 versus 6 by the GEE; in the horizontal-tilt group, $P < 0.001$ for the LCD1 versus 4; $P = 0.011$ for the LCD4 versus 6 by the GEE; Fig. 4A). The curvature of the LCD did not differ significantly according to the direction of the disc tilt in the healthy eyes ($P = 0.079$ by the GEE; Fig. 4A and Table 2). However, in the OAG eyes, the configuration of the anterior LC surface was clearly discriminated between the vertical- and horizontal-tilt groups. In the vertical-tilt group, the configuration was sloped toward the superior side, with a larger superior LC depth and a smaller inferior LCD ($P < 0.001$ for the LCD1 versus 7 by the GEE; Fig. 4B) when the slope also existed but was less distinct in healthy eyes with the vertically tilted discs ($P = 0.001$ for the LCD2 versus 5; $P = 0.010$ for the LCD2 versus 6 by the GEE; Fig. 4A).
TABLE 1. Demographics of the Healthy Subjects and Patients With OAG, Characterized According to Whether Their Optic Disc Is Tilted Vertically or Horizontally

<table>
<thead>
<tr>
<th></th>
<th>Healthy Eyes, n = 48</th>
<th>OAG Eyes, n = 66</th>
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<tbody>
<tr>
<td></td>
<td>Vertical Tilt</td>
<td>Horizontal Tilt</td>
</tr>
<tr>
<td>Age, y</td>
<td>47.6 ± 14.8</td>
<td>48.8 ± 12.1</td>
</tr>
<tr>
<td>Sex, males: females</td>
<td>16:7</td>
<td>9:16</td>
</tr>
<tr>
<td>Global RNFL thickness, μm</td>
<td>81.52 ± 8.57</td>
<td>87.32 ± 11.67</td>
</tr>
<tr>
<td>AL, mm</td>
<td>26.2 ± 1.2</td>
<td>26.8 ± 1.5</td>
</tr>
<tr>
<td>CCT, μm</td>
<td>579.75 ± 36.56</td>
<td>575.00 ± 21.68</td>
</tr>
<tr>
<td>Baseline IOP, mm Hg</td>
<td>13.6 ± 2.6</td>
<td>13.9 ± 2.7</td>
</tr>
<tr>
<td>IOP at optic disc scanning, mm Hg</td>
<td>12.2 ± 2.5</td>
<td>12.2 ± 1.8</td>
</tr>
<tr>
<td>Visual field MD, dB</td>
<td>-1.82 ± 1.99</td>
<td>-1.28 ± 1.19</td>
</tr>
<tr>
<td>Angle of tilt axis deviation, deg</td>
<td>9.4 ± 4.8</td>
<td>67.1 ± 15.6</td>
</tr>
<tr>
<td>Ovality index</td>
<td>1.44 ± 0.19</td>
<td>1.53 ± 0.21</td>
</tr>
<tr>
<td>Mean LCD, μm</td>
<td>461.12 ± 89.19</td>
<td>416.29 ± 101.79</td>
</tr>
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</table>

Except where indicated otherwise, data are mean ± SD values. *P values were calculated using the χ² test for categorical variables, and one-way ANOVA with the Sidak post hoc test for continuous variables. Statistically significant probability values are shown in bold.

Meanwhile, the slope in the OAG eyes with the horizontally tilted discs was clearly discriminated from that in the vertically tilted group, with the LCD being larger at the inferior ONH than at the superior ONH (P < 0.001 for the LCD2 versus 6 by the GEE; Figure 4B). This opposite pattern in the LCD slope between the different tilt groups was statistically significant (P < 0.001 by the GEE; Figure 4B, Table 2). Unlike in the healthy eyes, the central hump was less distinct and the LCD was generally larger in the OAG eyes (Figure 4B).

The difference in LCD between glaucomatous and healthy eyes was statistically significant at all locations in the vertical-tilt group, and at five locations in the horizontal-tilt group (LCD 3–7; Table 2). The LCD at the superior ONH region (LCD 1–2) was significantly larger in the vertical-tilt groups than in the horizontal-tilt groups in OAG eyes (Table 2).

Within the vertical-tilt groups, OAG eyes exhibited significant RNFL thinning in the superotemporal and inferotemporal sectors compared with the healthy eyes (all P < 0.001; Figure 5A). In the horizontal-tilt groups, significant RNFL thinning was found in OAG eyes in the inferotemporal (P < 0.001) sector (Figure 5B). The difference in the RNFL thickness profile between the healthy and the OAG eyes within the same disc-tilt groups was also significant when assessed by the GEE (all P < 0.001, Table 3). In both the healthy and the OAG eyes, the vertical-tilt groups had a thinner nasal and inferonasal RNFL thickness compared with the horizontal-tilt groups (Table 3). However, using the GEE, this difference was significant only in the healthy eyes (P = 0.044, Table 3).

DISCUSSION

The configuration of the anterior LC surface was evaluated in myopic tilted optic discs, and compared between eyes with vertical and horizontal optic disc tilt. It was found that the LCD profile differed according to the axis of the optic disc tilt, and that the different LCD patterns were associated with preferen-
Axonal fibers by twisting the axons around the optic disc, and could thus impose an additional stress on the optic disc.5,8 The opposite pattern in the LCD slope between the different tilt groups was statistically significant (*P < 0.001; by the GEE). The LCD with a red asterisk is significantly greater than that with a blue asterisk within the same subgroups (*P < 0.05; by the GEE). Data are means and 95% CIs.

Although the association between optic disc tilt or torsion and glaucomatous optic nerve damage is well established,6,11,15,41 the mechanism of glaucomatous damage according to the disc tilt or torsion has not been clearly understood. Stretching of axons toward the temporal side during the development of tilt has been suggested as the mechanism underlying glaucomatous damage in eyes with tilted optic discs.9,11,12,15,41 On the other hand, it is generally believed that optic disc torsion is caused by the rotation of the optic disc; however, the actual pattern of glaucomatous axonal damage does not support this hypothesis.5,8 In the present study, we postulated that optic disc torsion is another form of optic disc tilt that is centered on the oblique axis rather than being the result of optic disc rotation, and explored the mechanism underlying optic disc tilt or torsion and its association with glaucoma by investigating the structural characteristics of the LC in healthy and glaucomatous eyes with optic disc tilt.

First, to verify the presence of optic disc rotation, the configuration of the anterior LC surface was compared between eyes with different tilt axes. It was our assumption that if the optic disc had been rotated, the pattern of the anterior LC surface along the long axis would be comparable between eyes with vertically and horizontally oval discs. However, we found that the shape of the anterior LC surface along the long axis differed noticeably between the horizontal-tilt and vertical-tilt groups. In both healthy and glaucomatous eyes, the central hump was present only in association with vertically oval discs, while the central LC was somewhat excavated in horizontally oval discs. We postulate that the central hump is caused by the rotation of the optic disc, and could thus impose an additional stress on the optic disc; however, the actual pattern of glaucomatous axonal damage does not support this hypothesis.5,8

### Table 2. Anterior LCD Profiles in Seven Horizontal B-Scan Images in Each Group

<table>
<thead>
<tr>
<th>LCD, μm</th>
<th>Healthy Eyes, n = 48</th>
<th>OAG Eyes, n = 66</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vertical Tilt</td>
<td>Horizontal Tilt</td>
</tr>
<tr>
<td>LCD1</td>
<td>n = 23</td>
<td>n = 25</td>
</tr>
<tr>
<td>LCD2</td>
<td>n = 25</td>
<td></td>
</tr>
<tr>
<td>LCD3</td>
<td>n = 24</td>
<td></td>
</tr>
<tr>
<td>LCD4</td>
<td>n = 25</td>
<td></td>
</tr>
<tr>
<td>LCD5</td>
<td>n = 25</td>
<td></td>
</tr>
<tr>
<td>LCD6</td>
<td>n = 25</td>
<td></td>
</tr>
<tr>
<td>LCD7</td>
<td>n = 25</td>
<td></td>
</tr>
</tbody>
</table>

Comparisons were performed with the independent-samples t-test unless otherwise indicated. Values that were significant after Bonferroni correction (*P < 0.0071; 0.05/7) are shown in bold.

† The comparison between healthy and glaucomatous eyes within the vertical-tilt group.

‡ The comparison between healthy and glaucomatous eyes within the horizontal-tilt group.

§ This comparison was performed using the GEE. Values that were significant (*P < 0.05) are shown in bold.
rotation is actually the result of tilting centered on the deviated axis, with the amount determined by the rotational angle.

Then, we sought to identify the mechanism underlying the optic disc tilt by investigating the LCD profile from the superior to the inferior ONH in the eyes with different tilt axes. Interestingly, the LCD was larger superiorly than inferiorly in the vertical-tilt groups in a similar pattern to that found in previous studies. However, the horizontal-tilt groups exhibited the reverse pattern, with an increased LCD in the inferior regions. More intriguing result was that there was a spatial association between the LCD and the glaucomatous axonal damage. Temporally tilted optic discs were frequently accompanied by thinning of both the superotemporal and inferotemporal RNFL, while inferiorly tilted optic discs exhibited RNFL thinning most prominently in the inferior sectors, which concurs with the findings from previous studies. We speculate that these different patterns of glaucomatous damage are associated with the changes of LCD according to the optic disc tilt (Fig. 6).

![Figure 5](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933929/...)

**Figure 5.** Retinal nerve fiber layer thickness profiles in the vertical- (A) and horizontal-tilt (B) groups. (A) In the vertical-tilt group, the RNFL thinning was significant in the ST and IT sectors. (B) In the horizontal-tilt group, the RNFL thinning was significant in the ST, SN, and IT sectors; the thinning was most prominent in the IT sector in this group. The difference in the RNFL thickness profiles between the OAG eyes and the healthy eyes was significant in both tilt groups when analyzed using the GEE (all $P < 0.001$). Asterisks indicate significant differences between the groups: ($P \leq 0.0085$; $0.05/6$). Data are means and 95% CIs.

**Table 3.** Regional RNFL Thickness Profiles in Each Group

<table>
<thead>
<tr>
<th>Sectorial RNFL Thickness, µm</th>
<th>Healthy Eyes, $n = 48$</th>
<th>OAG Eyes, $n = 66$</th>
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<tbody>
<tr>
<td></td>
<td>Vertical Tilt</td>
<td>Horizontal Tilt</td>
</tr>
<tr>
<td></td>
<td>$n = 23$</td>
<td>$n = 25$</td>
</tr>
<tr>
<td>Temporal</td>
<td>74 ± 9.85</td>
<td>72.56 ± 17.13</td>
</tr>
<tr>
<td>Superotemporal</td>
<td>123.91 ± 23.43</td>
<td>119.2 ± 21.42</td>
</tr>
<tr>
<td>Superonasal</td>
<td>84.61 ± 18.05</td>
<td>89 ± 26.41</td>
</tr>
<tr>
<td>Nasal</td>
<td>44.99 ± 10.73</td>
<td>64.96 ± 14.77</td>
</tr>
<tr>
<td>Inferonasal</td>
<td>76.61 ± 14.45</td>
<td>91.84 ± 20.09</td>
</tr>
<tr>
<td>Inferotemporal</td>
<td>126.43 ± 24.20</td>
<td>122.92 ± 28.24</td>
</tr>
</tbody>
</table>

Comparisons were performed with the independent-samples t-test. Values that were significant after Bonferroni correction ($P \leq 0.0083$; $0.05/6$) are shown in bold.

* The comparison between healthy and glaucomatous eyes within the vertical-tilt group.
† The comparison between healthy and glaucomatous eyes within the horizontal-tilt group.
‡ This comparison was performed using the GEE. Values that were significant ($P < 0.05$) are shown in bold.
FIGURE 6. Two sample cases showing the different patterns of RNFL defect according to the tilt axis. (A) Color-disc photography of a glaucomatous eye with a vertically tilted optic disc. Parapapillary atrophy (PPA) exists at the temporal side, suggesting that the disc is tilted temporally. (B) Three-dimensional image constructed from SD-OCT optic disc scans of the same eye as in (A). The directions of forces exerted by the IOP (light blue arrow), axial elongation (dark blue arrow), and temporal optic disc tilt (red arrows) are shown. The combination of forces may be amplified at the temporal LC, and particularly in the superior and inferior regions, causing LC deformation and a corresponding RNFL defect in the superotemporal and inferotemporal sectors ([C], arrowheads). (D) Color-disc photography of a glaucomatous eye with a horizontally tilted optic disc. Parapapillary atrophy exists at the inferior side, suggesting an inferiorly tilted disc. (E) Three-dimensional SD-OCT image of the same eye as in (D). The directions of the forces exerted by the IOP (light blue arrow), axial elongation (dark blue arrow), and inferior optic disc tilt (red arrows) are shown. The combination of forces may be more concentrated at the inferior LC, inducing deformation in that portion thereof and damage to the inferior RNFL ([F], arrowheads).

6B). A sustained stress may damage the axons passing through the LC, beginning from the inferotemporal and superotemporal areas, which are the sites most vulnerable to damage (Fig. 6C). The stress from the elongation of the globe acts in the same direction as the optic disc tilt, which may increase the tensile stress within both the temporal peripapillary sclera and the temporal LC and further stretch the axons (Fig. 6B). In contrast, when the optic disc is tilted inferiorly, the LC may be subject to mechanical stress from the same sources but with different directions of action (Fig. 6E). While the globe elongation stretches the temporal nerve fibers, the inferior part of the optic disc may experience a larger stress because the stress from the optic disc tilt acts mainly in the inferior LC, simultaneously stretching and damaging the inferior axons (Fig. 6F). However, in this case, the directions of the two forces are different (one is temporal and the other is inferior), and the scleral tension may increase both temporally and inferiorly. Thus, the deformation of the LC may be of a lesser severity than that in the temporally tilted optic disc. This may at least partly explain why the LCD tended to be larger in the vertical-tilt groups than in the horizontal-tilt groups in this study. However, these speculations are yet to be supported and require validation through computational models and experiment.

Using time-domain OCT, Law et al. showed that the superior RNFL was thinned in nonglaucomatous eyes with inferiorly tilted optic discs relative to the normative database, which was not consistent with our finding. The discrepancy between these studies might be mainly due to the use of different OCT modalities and differences in the centering of the scan circle used when obtaining the circumpapillary RNFL scan. In the tilted discs, the pattern of RNFL thickness is comparable to the normative database when the scan circle is centered on the BMO rather than on the clinical disc margin. On the other hand, Cheung et al. showed that a superiorly displaced scan circle resulted in measurements of a thinner superior RNFL and a thicker inferior RNFL. It is possible that the scan circle had been centered on the clinical disc margin and displaced superiorly from the BMO in the study of Law et al. The scan circle was centered on the BMO in the present study, which may have resulted in the RNFL distribution in the nonglaucomatous disc-tilt group being similar to the normative curve.

The basic premise of this study was that the optic disc tilt results from remodeling of the ONH during myopia development. However, it must also be considered that the optic disc tilt may be associated with the variation in the individual developmental process. Although only myopic eyes were included in the study, the criterion allowed subjects with a very low degree of myopia to enroll, thus, it is possible that in some of those low myopic eyes, the mechanism of optic disc tilt was less associated with myopic globe elongation. However, in this study, only 4 eyes had a spherical refraction of greater than –1.0 D and the majority (92.1%, 105 of 114 eyes) had a spherical refraction of less than –2.0 D. Therefore, we believe that most of the eyes that were investigated in this study had tilted discs associated with myopia.

The reason for vertical tilting of the optic disc in some eyes and horizontal tilting in others remains unclear. Lee et al. postulated that the difference may be attributable to asymmetric elongation of the posterior pole. We speculate that regional differences in the peripapillary scleral properties could cause such asymmetric posterior-pole elongation near the ONH, which may ultimately lead to optic disc tilts with different axes.

In this study, the RNFL was thinner nasally and inferonasally in the vertical-tilt groups compared with the horizontal-tilt groups, both in the glaucoma and healthy eyes. At present, we cannot explain this difference. It may be due in part to the fact that the RNFL reflectance in the nasal quadrants is impeded by the angle of incidence of the illuminating beam, and...
therefore may affect the RNFL thickness measurement in this area.\textsuperscript{46–48} It is possible that this effect may be greater in vertically tilted discs because the retinal surface may have a greater slope on the nasal side of the optic disc in these eyes.

The present study was limited by the smallness of the sample. In addition, the nature of cross-sectional studies means that it was not possible to ascertain the causal relationships among optic disc tilt, LC deformation, and glaucomatous optic nerve damage. Further longitudinal studies are needed to elucidate this issue. On the other hand, the LCD profile was determined based on the visible end of the anterior LC surface, not on the anterior LC insertion. Thus, the LCD profile in this study may not accurately represent the true configuration of the entire LC. In addition, the deepest point of the anterior LC surface was obscured at times by vascular shadowing in the tilted optic discs. Although the eyes with this nonvisible deepest LC in more than two images were excluded from the study, the possibility of underestimation of the LCD in some eyes must be considered. Finally, the OAG patients included in the present study had an untreated IOP of less than 21 mm Hg, and so the results may not be generalizable to those with a higher untreated IOP. The criterion of an IOP of less than 21 mm Hg was chosen to minimize the influence of IOP on the LC tissue, since the aim was to determine the effect of optic disc tilt on the LCD.

In conclusion, the configuration of the anterior LC surface differed according to the tilt axis in myopic eyes with tilted discs. The data reported herein suggest that horizontally tilted discs are likely to be caused by tilting of the optic disc centered on an oblique axis, rather than by rotation. The different patterns of the LCD observed in the vertical- and horizontal-tilt groups corresponded with the preferential location of glaucomatous RNFL thinning. Both the superior and inferior RNFL were more likely to be damaged in eyes with vertically tilted optic discs, while the inferior region was most likely to be damaged in those with horizontally tilted optic discs. These findings suggest that the optic disc tilt axis could indicate the location of susceptibility to LC deformation and the potential site of subsequent glaucomatous axonal damage. The possibility of glaucomatous damage should be considered in both superior and inferior ONH regions in eyes with vertical disc tilt, with the probability being higher in the inferior region in those with horizontal disc tilt.

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