The Foveal Position Relative to the Optic Disc and the Retinal Nerve Fiber Layer Thickness Profile in Myopia

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Submitted: November 13, 2013
Accepted: January 17, 2014


Purpose. To evaluate retinal nerve fiber layer (RNFL) thickness profiles according to the foveal position relative to the optic disc in myopia

Methods. In 164 eyes of 164 healthy myopic subjects, the disc-foveal angle was defined as the angle between a horizontal line through the disc center and the line connecting the fovea and disc center in fundus photographs overlaid on Cirrus-HD optical coherence tomography (OCT) images. The quadrant/clock-hour based peripapillary RNFL thickness and differences between the inferior and superior (I-S) quadrant RNFL thicknesses were measured with OCT. RNFL thickness profiles were determined according to the disc-foveal angle and axial length (AL).

Results. As the disc-foveal angle increased (i.e., the fovea becomes more inferior to the optic disc), the superior RNFL decreased significantly (P = 0.003), whereas the inferior RNFL and I-S difference increased (P = 0.010 and P < 0.001, respectively). As the AL increased, the average and temporal RNFLs increased significantly (P = 0.013 and P < 0.001, respectively), and I-S difference was not affected (P = 0.251). The disc-foveal angle was significantly decreased with the distance between the fovea and the optic disc (P = 0.035). In multiple linear regression analysis, the disc-foveal angle was found to be a significant factor related to I-S differences, superior and inferior RNFL (all, P < 0.05) after adjusting for age, disc area, and AL.

Conclusions. The intrinsic foveal position relative to the optic disc was an essential determinant of normal RNFL thickness in myopia. In particular, it was associated with the vertical asymmetry of RNFL distribution.

Keywords: disc-foveal angle, retinal nerve fiber layer, RNFL distribution, myopia
surgery (LASIK or surface ablation, including laser epithelial keratomileusis [LASEK], epi-LASIK, or phakic intraocular lens insertion), between September and October, 2012 at the B & VIT Eye Center, Republic of Korea, patient charts were reviewed retrospectively. This study was performed according to the tenets of the Declaration of Helsinki, and the study protocol was approved by the institutional review/ethics boards of the Catholic University, Seoul St. Mary’s Hospital.

All subjects underwent a full ophthalmic examination, which included measuring the visual acuity (VA) and refraction, the intraocular pressure (IOP) using Goldmann applanonometry. AL using laser interference biometry (IOL Master; Carl Zeiss Meditec, Dublin, California), a diluted fundus examination, stereoscopy, and retinal photography using digital retinal cameras (CR-1 Mark II; Canon, Tokyo, Japan) after maximum pupil dilation and standard perimetry (24-2 Swedish interactive threshold algorithm, SAP, Humphrey field analyzer II; Carl Zeiss Meditec) and OCT (Cirrus high-definition [HD]-OCT; Carl Zeiss Meditec).

Inclusion criteria were a healthy optic nerve head without glaucomatous damage (i.e., no disc hemorrhage, thinning, or neural rim notching) and absence of any glaucomatous visual field (VF) defects. A glaucomatous VF change was defined as the consistent presence of a cluster of 3 or more points on the pattern deviation plot with a probability of occurring in <5% of the normal population or as having 1 point with the probability of occurring in <1% of the normal population and glaucoma hemifield test results outside the normal limits or a pattern standard deviation P of <5%.17

To rule out eyes with pathologic myopia, eyes with spherical equivalent less than −8.0 diopter (D) and pathologic retinal lesions, such as a lacquer crack, or Fuchs’ spot, were excluded. Eyes with concurrent disease other than refractive error, with a best-corrected VA < 20/20, an IOP > 21 mm Hg in either eye; a history of severe ocular trauma, intraocular or refractive surgery, or evidence of diabetic retinopathy; diabetic macular edema or other vitreoretinal disease in either eye; evidence of optic nerve or RNFL abnormality in either eye; media opacity, or a closed or occludable angle were also excluded. When both eyes were eligible, 1 eye was selected randomly for inclusion in the study.

Measurements of Disc–Foveal Angle, Optic Disc Tilt, Peripapillary Atrophy, and Distance From the Fovea to the Disc Center

Color retinal photographs were obtained using standard settings on a nondiabetic retinal camera (Cannon). The subjects were seated at the fundus camera with their chin in the chin rest and forehead against the forehead rest. The subjects’ eyes were aligned with the eye level mark on the forehead rest support by raising or lowering the chin rest. They were instructed to hold their heads in a vertical position throughout the photographic session. Using the eye to be photographed, each patient was instructed to look directly at the internal fixation target in the fundus camera, which was used as a marker for the foveal center.

Retinal photographs were evaluated independently and in random order and masked fashion, without knowledge of the clinical information by two of the authors (JAC and HYP). Optic disc tilt, the distance from the fovea to the disc center, was measured from the photographs using ImageJ version 1.40 software (National Institutes of Health, Bethesda, Maryland; http://rsb.info.nih.gov/ij/index.html). The average values of 2 authors, decided by deviation plot with a probability of occurring in <5% of the normal population or as having 1 point with the probability of occurring in <1% of the normal population and glaucoma hemifield test results outside the normal limits or a pattern standard deviation P of <5%.17

As shown in previous studies,14,24,25 both the RNFL peripapillary scan circle and the optic disc area are related to camera magnification in the fundus imaging system (p) and the optical dimension of the given eye (q). Therefore, we used the known magnification factor of 3.382 for the analysis of HD-OCT parameters (average/quadrant RNFL thickness), which is the same calculated value as that used for the Stratus OCT (Carl Zeiss Meditec) system (i.e., actual average RNFL thickness in a

Disc–Foveal Angle and RNFL Thickness

Investigative Ophthalmology & Visual Science

Vol. 55

No. 3

March 2014

1420

No. 3

March 2014

1420

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Data Analysis

The distribution of all variables was examined for normality using Shapiro-Wilk normality testing. To evaluate the intervisit reproducibility of the disc–foveal angle, 30 randomly selected patients from the enrolled patients underwent 2 retinal photographs on separate days. Intervisit and interobserver reproducibility values were calculated using the intraclass correlation coefficient (ICC) from a 2-way mixed effect model.

All participants were divided into 2 groups according to disc–foveal angle. The cutoff value for the degree of disc–foveal angle classification was based on the median value. Independent Student t-tests for independent variables were used to compare means between subjects with a greater disc–foveal angle and those with a lesser disc–foveal angle.

The relationships between the average/quadrant-based mean RNFL thickness and the disc–foveal angle and AL were subjected to linear regression analysis. In addition, the correlations between disc–foveal angle and ocular factors such as AL, distance from the fovea to the disc center, and tilt ratio were assessed.

To assess the determinant factors of the RNFL distribution, multiple linear regression analyses were performed. The dependent variable was the I-S difference, that is, the superior, inferior, and temporal quadrant RNFL thickness. The independent variables were age, AL, disc area, and disc–foveal angle. Statistical analyses were performed using SPSS for Windows (Microsoft, Redmond, Washington) version 14.0 (SPSS, Chicago, Illinois) and MedCalc version 9.6 (Mariakerke, Belgium). P values < 0.05 were considered statistically significant.

Results

A total of 164 eyes of 164 young participants who met the inclusion and exclusion criteria were analyzed (mean age, 28.12 ± 6.40 years; 41.3% men; all Koreans). The initial IOP was 15.04 ± 2.60 mm Hg, and the mean corneal thickness was 536.83 ± 6.40 mm (range, 510.0–560.0 mm). The mean spherical equivalent and AL were –4.48 ± 2.06 D (range, –8.00 to –0.38 D) and 25.48 ± 1.06 mm (range, 22.86–28.97 mm), respectively. The average optic disc area was 1.86 ± 0.36 mm² (range, 1.07–3.01 mm²), and the average RNFL thickness was 86.0 ± 1.82 μm (range, 76.39–125.26 μm).

The average disc–foveal angle was 6.08° ± 3.48° (range, –1.11° to 14.97°). As shown in the mean distribution of the disc–foveal angle (Fig. 2), most values were positive and showed normal distributions upon Shapiro-Wilk normality testing (P = 0.128). The measurement of disc–foveal angle showed excellent interobserver (CJA and PHY) and intervisit reproducibility. ICC, 0.965 (95% confidence interval: 0.927–0.984) and ICC 0.933 (95% confidence interval: 0.864–0.935), respectively.

To characterize the disc–foveal angle, we compared the ocular variables between eyes with a greater disc–foveal angle (>6.03°; indicating a more inferior foveal position relative to the optic disc) and those with a lesser disc–foveal angle (<6.03°; indicating a foveal position more parallel to the optic disc) (Table 1). In eyes with a greater disc–foveal angle, the superior RNFL was marginally thinner (P = 0.087), whereas the inferior RNFL was thicker in eyes with a greater disc–foveal angle than in eyes with a lesser disc–foveal angle (P = 0.041). The I-S difference differently significantly between groups, with an inverted value in eyes with a lesser disc–foveal angle (P = 0.002). In the OCT profiles of the 164 participants, the superior RNFL decreased significantly (r = –0.224, P = 0.005), and the inferior RNFL and I-S differences increased significantly (r = –0.196, P = 0.010; r = 0.336, P < 0.001) with an increase in the disc–foveal angle (Fig. 3).

The linear regression analysis of disc–foveal angle and clock-hour-based RNFL thickness showed that RNFL thicknesses from 7 to 1 o’clock decreased (statistical significance at 8 and 12 o’clock; P = 0.016 and P < 0.001, respectively), and RNFL thicknesses from 2 to 6 o’clock increased (statistical signifi-
cance at 5 and 6 o'clock; $P = 0.002$ and $P = 0.008$, respectively) with an increase in the disc–foveal angle (Table 2).

In terms of AL, the average and temporal RNFL increased significantly ($r = 0.194$, $r^2 = 0.038$, $P = 0.013$; and $r = 0.408$, $r^2 = 0.161$, $P < 0.001$, respectively), while the I-S difference was not associated with AL ($r = -0.094$, $r^2 = 0.003$, $P = 0.231$) (Fig. 4).

The distance from the fovea to the disc center was increased with AL and disc tilt ($r = 0.155$, $P = 0.041$; and $r = 0.336$, $P < 0.001$, respectively). The disc–foveal angle decreased significantly with the distance from the fovea to the disc center ($r = -0.161$, $P = 0.033$).

After multiple linear regression analysis, the disc–foveal angle was found to be the significant factor related to the I-S difference ($P < 0.001$) after controlling for age, disc area, and AL. The disc–foveal angle also significantly affected the superior and inferior quadrant RNFL thickness ($P = 0.004$ and $P = 0.004$, respectively). Regarding temporal quadrant RNFL thickness, AL was found to be a significant determinant after multiple linear regression analysis ($P < 0.001$) (Table 3).

**DISCUSSION**

This study demonstrated that the foveal position relative to the optic disc was a significant determinant of the RNFL distribution in healthy myopic subjects (Table 3 and Fig. 5). Whereas AL particularly affected the temporal-side RNFL, the relative foveal position was associated with the vertical asymmetry of RNFL distribution. The disc–foveal angle was also affected by the distance between the fovea and the disc center. There is a wide range of normal RNFL thickness variation, which is affected by age, ethnicity, AL, and optic disc area.\textsuperscript{3,5,25} To the best of our knowledge, this is the first study to characterize the relative foveal position as a significant determinant of the normal RNFL distribution in relation to other known determinant factors.

### Table 1. Posterior Pole Characteristics of Subgroups Classified by Disc–Foveal Angle

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Greater Disc–Foveal Angle ($\geq 6.03^\circ$)</th>
<th>Lesser Disc–Foveal Angle ($&lt; 6.03^\circ$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>82</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>Disc–foveal angle</td>
<td>8.83 ± 2.23</td>
<td>3.28 ± 1.92</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spherical equivalent, D</td>
<td>-5.16 ± 2.22</td>
<td>-4.68 ± 2.82</td>
<td>0.218</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>25.68 ± 1.13</td>
<td>25.59 ± 1.22</td>
<td>0.589</td>
</tr>
<tr>
<td>Distance from fovea to disc center, mm</td>
<td>6.36 ± 0.37</td>
<td>6.44 ± 0.41</td>
<td>0.153</td>
</tr>
<tr>
<td>Optic disc area, mm$^2$</td>
<td>1.94 ± 0.40</td>
<td>2.00 ± 0.35</td>
<td>0.298</td>
</tr>
</tbody>
</table>

| RNFL profiles                  |                                               |                                           |       |
|--------------------------------|                                               |                                           |       |
| Average RNFL thickness, μm     | 98.86 ± 8.04                                  | 98.50 ± 9.29                              | 0.783 |
| Quadrant analysis, μm          |                                               |                                           |       |
| Superior                       | 120.08 ± 14.39                                | 123.82 ± 14.34                            | 0.087 |
| Nasal                          | 65.00 ± 10.31                                 | 66.62 ± 12.84                             | 0.361 |
| Inferior                       | 125.98 ± 15.31                                | 120.94 ± 16.95                            | 0.041 |
| Temporal                       | 84.52 ± 18.80                                 | 83.37 ± 18.20                             | 0.685 |
| Inferior-superior difference   | 5.89 ± 17.10                                  | -2.89 ± 19.86                             | 0.002 |

Comparison was done using Student $t$-test.

RNFL, retinal nerve fiber layer.

Data are means ± SD, unless indicated otherwise.
To measure the position of the fovea relative to the optic disc, we used the disc–foveal angle determined by fundus photography, which is the standard method for quantifying cyclotropia in strabismus clinics. The effect of static ocular counter-roll, a compensatory torsional eye movement during head tilt, is reported to remain within 1°, provided the head tilt was <5°. The disc–foveal angle is not affected by laterality, sex, or age. However, small amounts of changes in physiological ocular rotation exist among each test session, which may affect the intertest measurement reproducibility of peripapillary RNFL thicknesses. Therefore, in this study, we compensated for the potential effect of the ocular rotation on the disc–foveal angle by using fundus photographs overlaid on spectral-domain (SD)-OCT images (Fig. 1). Similar to results in previous studies, the mean disc–foveal angle of our study participants was 6.08° ± 3.48°. As shown in Figure 2, there was considerable variation in the normal disc–foveal angle, and most values were positive, which indicates that the fovea is positioned below the optic disc.

The development and progression patterns in the superior and inferior retina differ in glaucomatous damage. The neuroretinal rim in normal eyes is broadest on the inferior side. In addition, the RNFL thickness on the inferior side tends to be slightly thicker than on the superior side in normal subjects. However, the superior VF corresponding to the inferior retina is involved more frequently in the early stages of glaucoma with faster progression than the inferior VF. In addition, the inferotemporal meridian was found to be the most frequent location where RNFL progression was detected.

The regional susceptibility of the inferior temporal optic disc to glaucomatous damage appears to be associated with the inferior foveal position relative to the optic disc. Hood et al. suggested that, because of the characteristic foveal position, the inferior temporal side of the optic disc is more crowded, with a higher density of retinal ganglion cell axons than other disc regions, rendering the region more vulnerable to glaucomatous damage. In this study, as the fovea became more parallel with the optic disc, the superior RNFL increased significantly (P = 0.003), whereas the inferior RNFL and I–S differences decreased (P = 0.010 and P < 0.001, respectively) (Fig. 3). In addition, eyes with a more inferior foveal position relative to the optic disc (greater disc–foveal angle) had a thicker inferior RNFL and a greater I–S difference than eyes with the fovea positioned parallel to the optic disc (lesser disc–foveal angle) (Table 1). Our results support the hypothesis that the relative foveal position is one of the key factors determining the RNFL distribution.

Previous studies have found that myopia redistributes the RNFL with axial elongation. With increased AL, there is temporalization of the retinal vessels and thickening of the temporal RNFL. In agreement with this finding, we observed thickening of the average RNFL and on the temporal side with increased AL (P = 0.001 and P < 0.001, respectively) (Fig. 4). Consistent with the previous studies where the Littmann formula was used to eliminate the effect of ocular magnification related to the AL, we found that the average RNFL thickness increased with AL. The thicker average RNFL thickness in myopic eyes compared to nonmyopic eyes may be related to the overshooting effect related to the adjustment for ocular magnification. In addition, eyes with a larger retinal surface area (i.e., eyes with long AL) may retain more RNFL thickness.

**Table 2.** Linear Regression Analysis of Disc–Foveal Angle and Clock-Hour-Based Retinal Nerve Fiber Layer Thickness

<table>
<thead>
<tr>
<th>Clock Hour</th>
<th>R</th>
<th>R²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>−0.075</td>
<td>0.006</td>
<td>0.322</td>
</tr>
<tr>
<td>12</td>
<td>−0.308</td>
<td>0.095</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1</td>
<td>−0.074</td>
<td>0.005</td>
<td>0.352</td>
</tr>
<tr>
<td>2</td>
<td>0.065</td>
<td>0.004</td>
<td>0.396</td>
</tr>
<tr>
<td>3</td>
<td>0.032</td>
<td>0.001</td>
<td>0.671</td>
</tr>
<tr>
<td>4</td>
<td>0.109</td>
<td>0.012</td>
<td>0.155</td>
</tr>
<tr>
<td>5</td>
<td>0.238</td>
<td>0.056</td>
<td>0.002</td>
</tr>
<tr>
<td>6</td>
<td>0.198</td>
<td>0.039</td>
<td>0.008</td>
</tr>
<tr>
<td>7</td>
<td>−0.017</td>
<td>0.000</td>
<td>0.825</td>
</tr>
<tr>
<td>8</td>
<td>−0.182</td>
<td>0.033</td>
<td>0.016</td>
</tr>
<tr>
<td>9</td>
<td>−0.094</td>
<td>0.009</td>
<td>0.215</td>
</tr>
<tr>
<td>10</td>
<td>−0.102</td>
<td>0.010</td>
<td>0.180</td>
</tr>
</tbody>
</table>

**Figure 4.** Scatterplots show the relationship between the axial length and RNFL thickness measured using Cirrus-OCT. The inferior-superior difference was defined as the inferior quadrant RNFL thickness minus the superior quadrant RNFL thickness in an individual. Pearson’s correlation coefficient R values are shown.
than normal eyes, considering that optic disc size is positively correlated with AL and that the larger optic disc is associated with more retinal nerve fiber axons, as shown in the previous histomorphometric study.40

Intriguingly, we also observed that the position of the fovea becomes parallel to the optic disc as the distance between the fovea and disc center increases \((P = 0.033)\), which may suggest that there is asymmetrical enlargement in the posterior sclera between the superior and inferior regions in general axial myopia. The posterior sclera is more immature, produces more collagen, and is more extensible than the anterior and equatorial scleral regions, which makes it particularly susceptible to myopic changes.41 The posterior sclera is the outer shell of the posterior pole and changes in the posterior sclera are reflected in the posterior pole, as shown in studies that analyzed outer deformities of the posterior sclera in cross-sectional images of the macula and optic disc.15,16 Further studies using other imaging devices, such as swept-source OCT and magnetic resonance imaging (MRI) are needed to elucidate the changes in the posterior sclera with axial elongation in general myopia.

One of the limitations of this study was that it was clinically based and not population-based screening. The participants were all Koreans of similar age. In this study, participants with concurrent ophthalmic abnormalities or with a best-corrected VA of \(<20/20\) were excluded. Furthermore, by virtue of our study design, the information regarding the shifts of disc–foveal angle with progressive vision loss cannot be addressed. Future studies of ocular rotational orientation in imaging eyes with vision loss or progressive vision loss are necessary. In addition, most participants were myopic, and we adjusted the measurement of RNFL thickness by using the Littmann formula21 to remove the potential bias of AL-related ocular magnification. However, a population-based study including individuals with various refractive errors, as well as different ethnicities and ages, is needed to confirm our findings.

In summary, the foveal position relative to the optic disc was a significant determinant of the normal RNFL thickness profile. The relative position of the fovea was affected by the distance between the fovea and disc center. Knowledge of the normal anatomical variation associated with the relative foveal position will help to identify and follow glaucoma patients.

### Table 3. Multiple Linear Regression Analysis of Demographics and Clinical Variables: Effect on Various Retinal Nerve Fiber Layer Thickness Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>I-S Difference</th>
<th>Superior Quadrant</th>
<th>Inferior Quadrant</th>
<th>Temporal Quadrant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regression Coefficient (SEM)</td>
<td>Regression Coefficient (SEM)</td>
<td>Regression Coefficient (SEM)</td>
<td>Regression Coefficient (SEM)</td>
</tr>
<tr>
<td>Age</td>
<td>0.083 (0.203)</td>
<td>-0.238 (0.157)</td>
<td>-0.154 (0.177)</td>
<td>-0.332 (0.181)</td>
</tr>
<tr>
<td>Disc area</td>
<td>1.091 (3.700)</td>
<td>7.593 (2.857)</td>
<td>8.684 (3.228)</td>
<td>-5.054 (3.287)</td>
</tr>
<tr>
<td>Axial length</td>
<td>-2.622 (1.231)</td>
<td>0.187 (0.950)</td>
<td>-2.435 (1.073)</td>
<td>7.564 (1.093)</td>
</tr>
<tr>
<td>Disc–foveal angle</td>
<td>1.886 (0.396)</td>
<td>-0.882 (0.305)</td>
<td>1.004 (0.345)</td>
<td>-0.272 (0.351)</td>
</tr>
</tbody>
</table>

*I-S difference was designated as the difference between the inferior and superior retinal nerve fiber layer (RNFL) thicknesses.*
References
