Parapapillary Gamma Zone and Axial Elongation–Associated Optic Disc Rotation: The Beijing Eye Study

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PURPOSE. The parapapillary gamma zone has been defined as the parapapillary region without Bruch's membrane. We examined which morphologic parameters are associated with the presence and size of the parapapillary gamma zone.

METHODS. Using fundus photographs and spectral-domain optical coherence tomographic images of the optic nerve head in the population-based Beijing Eye Study, we determined parapapillary gamma zone width, macular Bruch's membrane length, optic disc–fovea distance, the angle of horizontal optic disc rotation, the angle of vertical optic disc rotation, and the ratio of the vertical-to-horizontal disc diameter.

RESULTS. The study included 2068 individuals with a mean age of 63.0 ± 9.0 years (range, 50–91 years), and mean axial length was 23.2 ± 1.0 mm (range, 18.96–28.87 mm). In multivariate analysis, larger width of parapapillary gamma zone was associated with more marked vertical optic disc rotation ($P < 0.01$; standardized correlation coefficient $b$, 0.15; nonstandardized correlation coefficient $B$, 0.02; 95% confidence interval [CI], 0.02, 0.05), more marked horizontal optic disc rotation ($P = 0.02$; $b$, 0.05; $B$, 0.01; 95% CI, 0.001, 0.01), longer axial length ($P = 0.01$; $b$, 0.07; $B$, 0.02; 95% CI, 0.01, 0.04), longer horizontal optic disc diameter ($P = 0.02$; $b$, 0.05; $B$, 0.06; 95% CI, 0.01, 0.12), longer disc–fovea distance ($P < 0.001$; $b$, 0.25; $B$, 0.22; 95% CI, 0.18, 0.27), higher degree of fundus tessellation ($P = 0.05$; $b$, 0.17; $B$, 0.04; 95% CI, 0.03, 0.0), and thinner subfoveal choroidal thickness ($P < 0.001$; $b$, −0.13; $B$, 0.000; 95% CI, −0.001, 0.000). Parapapillary gamma zone width was not significantly associated with macular Bruch's membrane length ($P = 0.72$), disc–fovea angle ($P = 0.62$), age ($P = 0.62$), or sex ($P = 0.46$).

CONCLUSIONS. The parapapillary gamma zone was associated with an axial elongation–induced rotation of the optic disc mainly around the vertical disc axis, leading to a stretching of the temporal parapapillary scleral flange. Because macular Bruch's membrane length was independent of axial elongation, it leaves the temporal parapapillary region with an uncovered Bruch's membrane (i.e., parapapillary gamma zone develops).

Keywords: parapapillary gamma zone, optic disc, optic disc rotation, parapapillary atrophy, Bruch's membrane, myopia, Beijing Eye Study

The parapapillary gamma zone has recently been defined as the parapapillary region free of Bruch's membrane.1,2 On its inner side, it is adjacent to the peripapillary ring of the optic nerve head. On its outer border, the gamma zone is in contact either with the parapapillary beta zone, if a beta zone is present, or with the parapapillary alpha zone. In the beta zone, Bruch’s membrane is devoid of retinal pigment epithelium.3,4 The alpha zone is characterized by Bruch's membrane covered by an irregular retinal pigment epithelium. Previous studies revealed that the beta zone was correlated stronger with glaucomatous optic neuropathy than with axial myopia.1,5 A recent investigation suggested that the development of beta zone might be associated with a centrifugal slippage of the retinal pigment epithelium on Bruch’s membrane if the intraocular pressure rises.6 In contrast to the beta zone, the gamma zone was correlated stronger with axial myopia than with glaucomatous optic nerve damage.1,5 Because the factors associated with the development of gamma zone have remained elusive thus far, we conducted this study to assess which factors may be connected with the presence and size of the parapapillary gamma zone.

MATERIALS AND METHODS

Study Participants

The Beijing Eye Study 2011 was a population-based cross-sectional study in northern China. The Medical Ethics Committee of the Beijing Tongren Hospital approved the study protocol, and all participants gave informed consent. The
Beijing Eye Study was carried out in five communities in the urban district of Haidian in the north of central Beijing and in three communities in the village area of Yufa of the Daxing District south of Beijing. The only eligibility criterion for inclusion into the study was an age of 50+ years. Of 4405 eligible individuals, 3468 (response rate, 78.8%) individuals participated in the survey. Among the 3468 subjects, 1635 (47.1%) individuals lived in the rural region and 1833 (52.9%) individuals lived in the urban region. Mean age was 64.6 ± 9.8 years (median, 64 years; range, 50–93 years), mean refractive error was −0.22 ± 2.12 diopters (D) (median, −0.25 D; range, −22.00 to +7.00 D), and mean axial length was 23.3 ± 1.1 mm (median, 23.1 mm; range, 18.96–30.88 mm). Mean prevalence of glaucoma was 4.3% (95% confidence interval [CI], 3.6, 5.0), diabetic retinopathy was 2.4% (95% CI, 1.9, 2.9), and retinal vein occlusions was 2.9% (95% CI, 2.3, 3.4). The study has already been described in detail previously.7,8

Methods
All study participants underwent an interview with standardized questions on their level of education, physical activity, and known major systemic diseases. An ophthalmic examination included measurement of best corrected visual acuity, slit-lamp examination of the anterior segment, tonometry, biometry using optical low-coherence reflectometry (Lensstar 900; CR6-45NM; Canon, Inc., Tokyo, Japan), macula, and optic disc (fundus camera type CR6-45NM; Canon, Inc., Tokyo, Japan).

Using spectral-domain optical coherence tomography (OCT) (Spectralis; Heidelberg Engineering Co., Heidelberg, Germany) with the enhanced depth imaging modality, we obtained images of the fovea and of the optic nerve head. Seven sections (each comprising 100 averaged scans) were obtained in a $5 \times 50'$ large rectangle centered onto the fovea. Using the scan running through the fovea, we measured the thickness of the subfoveal choroid and the length of Bruch’s membrane from the fovea to the end of Bruch’s membrane in direction of the optic nerve head (Figs. 1, 2).9,10 We additionally determined the length of a parapapillary region free of Bruch’s membrane (i.e., parapapillary gamma zone) in a subset of eyes.

Using the fundus photographs, we measured the distance between the fovea and the optic nerve head center, and we measured the angle between the disc center–fovea line and the horizontal.11 On the optic disc photographs, we determined, on a line connecting the disc center and the fovea, the width of the parapapillary beta/gamma zone defined as the parapapillary zone with visible sclera.12,13 On the photographs, we also measured the area of parapapillary beta/gamma zone defined as the parapapillary zone with visible sclera (Fig. 3). We corrected the image magnification caused by the optic media of the eye and by the fundus camera using the Littmann-Bennett method.14,15

The rotation of the optic disc around the vertical optic disc axis and the optic disc rotation around the horizontal disc axis were assessed on OCT scans that ran through the center on the optic nerve head in the horizontal direction and in the vertical direction (Fig. 2).16 We measured the angle between the line connecting the ends of Bruch’s membrane and the horizontal for the assessment of the rotation around the vertical axis, and we measured the angle between the line connecting the ends of Bruch’s membrane and the vertical for the assessment of the rotation around the horizontal axis.

The degree of fundus tessellation as assessed on the fundus photographs and on the optic disc photographs was differentiated between grade 0 for “no tessellation” and grade 3 for “marked tessellation.” The technique has been described in detail recently.17

Statistical Analysis
A commercially available statistical software package (SPSS for Windows, version 22.0; IBM-SPSS, Chicago, IL, USA) was applied for the statistical analysis. We first calculated the mean and SDs of the main outcome parameters. In a second step of
the analysis, we performed univariate analyses of potential associations between the width of the parapapillary gamma zone and other ocular and general parameters. In a third step, we carried out a multivariate analysis, with gamma zone width as the dependent variable and, as independent variables, all those parameters that were significantly associated with gamma zone width in the univariate analysis. We then dropped, step by step, those parameters from the list of

FIGURE 2. Optical coherence tomogram of the optic nerve head. The rotation of the optic disc around the vertical disc axis was determined as angle between the horizontal (green line) and a line (red line) connecting the ends of Bruch’s membrane in the horizontal meridian of the optic disc. The higher-magnification scale in the vertical direction compared with the horizontal direction was taken into account.

FIGURE 3. Fundus photograph of an optic nerve head and the corresponding optical coherence tomograms. The area of the parapapillary beta/gamma zone (area surrounded by a blue line) on the fundus photograph is outlined. Vertical pink short strokes: Marks on the optical coherence tomograms and, correspondingly, on the fundus photograph.
Table 1. Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean ± SD</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63.0 ± 9.0</td>
<td>61.0</td>
<td>50 to 91</td>
</tr>
<tr>
<td>Refractive error, diopeters</td>
<td>−0.02 ± 1.68</td>
<td>+0.25</td>
<td>−12.50 to +7.00</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>23.2 ± 1.00</td>
<td>23.11</td>
<td>18.96 to 28.87</td>
</tr>
<tr>
<td>Vertical-to-horizontal disc diameter ratio</td>
<td>1.08 ± 0.15</td>
<td>1.07</td>
<td>0.53 to 1.72</td>
</tr>
<tr>
<td>Disc center-fovea angle against the horizontal, deg</td>
<td>7.77 ± 3.52</td>
<td>7.64</td>
<td>−16.6 to 23.5</td>
</tr>
<tr>
<td>Width of parapapillary gamma zone, mm</td>
<td>0.11 ± 0.31</td>
<td>0.00</td>
<td>0.00 to 2.54</td>
</tr>
<tr>
<td>Macular Bruch’s membrane length, mm</td>
<td>3.74 ± 0.37</td>
<td>3.75</td>
<td>2.04 to 5.19</td>
</tr>
<tr>
<td>Disc center-fovea distance, mm</td>
<td>4.74 ± 0.34</td>
<td>4.73</td>
<td>5.76 to 6.53</td>
</tr>
<tr>
<td>Disc radius, mm</td>
<td>0.90 ± 0.09</td>
<td>0.90</td>
<td>0.60 to 1.30</td>
</tr>
</tbody>
</table>

independent parameters, which either showed a high collinearity or which were no longer significantly associated with gamma zone width. All P values were 2-sided and were considered statistically significant when the values were <0.05. We calculated the standardized correlation coefficient β, the nonstandardized correlation coefficient B, and its 95% CI. Inclusion criteria for the present study were the availability of measurements of the vertical and horizontal optic disc rotation, disc-fovea distance, width of gamma zone, axial length, and horizontal and vertical disc diameters.

Results

The study included 2068 individuals with a mean age of 63.0 ± 9.0 years (range, 50–91 years) and a mean refractive error of −0.02 ± 1.68 D (range, −12.50 to +7.00 D; Table 1). Mean axial length was 23.2 ± 1.00 mm, mean width of parapapillary gamma zone was 0.11 ± 0.31 mm, mean macular Bruch’s membrane length was 3.74 ± 0.37 mm, and mean disc center-fovea distance was 4.74 ± 0.34 mm. Mean disc radius was 0.90 ± 0.09 mm, with macular Bruch’s membrane length plus parapapillary gamma zone width plus disc radius adding up to disc center-fovea distance.

The participants (n = 2068 or 59.6%) compared with the nonparticipants (n = 1400) were significantly younger (63.0 ± 9.0 vs. 67.0 ± 10.4 years; P < 0.001) and had a significantly shorter axial length (23.2 ± 1.0 vs. 23.4 ± 1.4 mm; P < 0.001). Both groups did not differ significantly in sex (P = 0.43).

In univariate analysis, a larger width of the gamma zone was associated with older age (P < 0.001), male sex (P = 0.001), longer axial length (P < 0.001), longer horizontal and vertical disc diameter (P < 0.001), more marked disc rotation around the vertical axis (P < 0.001), higher vertical-to-horizontal disc diameter ratio (P < 0.001), longer disc-fovea distance (P < 0.001), higher degree of fundus tessellation (P < 0.001), and thinner subfoveal choroidal thickness (Table 2).

In the multivariate analysis, we first dropped from the list of independent parameters the parameters of age (P = 0.62) and sex (P = 0.46) due to lack of significance and the parameter of vertical disc diameter due to a high variance inflation factor of 15.2, and we eventually dropped the parameter of vertical-to-horizontal disc diameter ratio due to a lack of significance (P = 0.85). In the final model, larger width of the parapapillary gamma zone was associated (regression coefficient r = 0.50) with more marked vertical optic disc rotation (P < 0.001), more marked horizontal optic disc rotation (P = 0.02), longer axial length (P = 0.010), longer horizontal optic disc diameter (P = 0.02), longer disc-fovea distance (P < 0.001), higher degree of fundus tessellation (P = 0.03), and thinner subfoveal choroidal thickness (P < 0.001; Table 3). If glaucoma was added to the model, it was not significantly associated with gamma zone width (P = 0.51).

If instead of the width of the parapapillary gamma zone, the area of the gamma zone was taken, a larger gamma zone area was associated (regression coefficient r = 0.47) with more

Table 2. Associations (Univariate Analysis) Between the Width of the Parapapillary Gamma Zone and Other Ocular and Systemic Parameters in the Beijing Eye Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>P Value</th>
<th>Standardized Correlation Coefficient β</th>
<th>Nonstandardized Correlation Coefficient B</th>
<th>95% CI of B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>&lt;0.001</td>
<td>0.13</td>
<td>0.004</td>
<td>0.003, 0.006</td>
</tr>
<tr>
<td>Sex</td>
<td>0.001</td>
<td>−0.07</td>
<td>−0.04</td>
<td>−0.07, −0.02</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>&lt;0.001</td>
<td>0.10</td>
<td>0.09, 0.12</td>
<td></td>
</tr>
<tr>
<td>Refractive error, D</td>
<td>&lt;0.001</td>
<td>−0.32</td>
<td>−0.06</td>
<td>−0.07, −0.05</td>
</tr>
<tr>
<td>Cylindrical refractive error, D</td>
<td>0.55</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horizontal optic disc diameter, mm</td>
<td>&lt;0.001</td>
<td>0.21</td>
<td>0.21, 0.31</td>
<td></td>
</tr>
<tr>
<td>Optic disc rotation around vertical axis, deg</td>
<td>&lt;0.001</td>
<td>0.21</td>
<td>0.13, 0.27</td>
<td></td>
</tr>
<tr>
<td>Vertical optic disc diameter, mm</td>
<td>&lt;0.001</td>
<td>0.20</td>
<td>0.14, 0.27</td>
<td></td>
</tr>
<tr>
<td>Optic disc rotation around horizontal axis, deg</td>
<td>&lt;0.001</td>
<td>0.20</td>
<td>0.02, 0.03</td>
<td></td>
</tr>
<tr>
<td>Vertical-to-horizontal optic disc diameter ratio</td>
<td>&lt;0.001</td>
<td>−0.20</td>
<td>−0.28, −0.11</td>
<td></td>
</tr>
<tr>
<td>Optic disc center-fovea angle against the horizontal, deg</td>
<td>0.62</td>
<td>−0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optic disc center-fovea distance, mm</td>
<td>&lt;0.001</td>
<td>0.33</td>
<td>0.29, 0.37</td>
<td></td>
</tr>
<tr>
<td>Macular Bruch’s membrane length, mm</td>
<td>0.72</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fundus tessellation, deg</td>
<td>&lt;0.001</td>
<td>0.09</td>
<td>0.08, 0.10</td>
<td></td>
</tr>
<tr>
<td>Subfoveal choroidal thickness, µm</td>
<td>&lt;0.001</td>
<td>−0.01</td>
<td>−0.001, −0.001</td>
<td></td>
</tr>
<tr>
<td>Intraocular pressure, mm Hg</td>
<td>0.12</td>
<td>0.05</td>
<td>0.004</td>
<td>−0.001, 0.009</td>
</tr>
</tbody>
</table>
marked vertical optic disc rotation ($P < 0.001; \beta, 0.12; B, 0.03$; 95% CI, 0.02, 0.04), longer horizontal optic disc diameter ($P < 0.001; \beta, 0.07; B, 0.47$; 95% CI, 0.21, 0.73), longer disc–fovea distance ($P < 0.001; \beta, 0.24; B, 0.38$; 95% CI, 0.30, 0.47), higher degree of fundus tessellation ($P < 0.001; \beta, 0.18; B, 0.08$; 95% CI, 0.06, 0.11), and thinner subfoveal choroidal thickness ($P < 0.001; \beta, -0.13; B, -0.001; 95% CI, -0.001, 0.000$), whereas the association with a more marked horizontal optic disc rotation ($P = 0.055; \beta, 0.04; B, 0.01$; 95% CI, 0.00, 0.02) and longer axial length ($P = 0.058; \beta, 0.05; B, 0.03$; 95% CI, -0.001, 0.006) were no longer statistically significant.

Measurements of gamma zone obtained from OCT images were available for 217 eyes. Gamma zone width measured by OCT was significantly smaller than gamma zone width as measured on the fundus photographs (0.09 ± 0.27 vs. 0.11 ± 0.31 mm; $P < 0.001$). The difference between both parameters could be explained by the measurements on the fundus photographs including the gamma zone and (to a relatively small amount of 0.02 mm) the width of the beta zone. If measurements of the gamma zone obtained from OCT images instead of measurements obtained from the optic disc photographs were used for the statistical analysis, similar results were obtained. Longer length of the gamma zone was significantly associated with a more marked rotation of the optic disc around the vertical axis ($P < 0.001; \beta, 0.16; B, 10.4$; 95% CI, 3.6, 17.2), longer axial length ($P < 0.001; \beta, 0.30; B, 4.4$; 95% CI, 0.36, 7.6), and longer disc–fovea distance ($P < 0.001; \beta, 0.36; B, 170; 95% CI, 95, 247$). If glaucoma was added to the model, it was not significantly associated with gamma zone width ($P = 0.80$).

**DISCUSSION**

In our population-based study on adult Chinese, a larger width of the parapapillary gamma zone was associated with more marked optic disc rotation around the vertical axis ($P < 0.001$) and around the horizontal axis ($P = 0.02$), longer axial length ($P = 0.01$), longer horizontal optic disc diameter ($P = 0.02$), longer disc–fovea distance ($P < 0.001$), higher degree of fundus tessellation ($P = 0.03$), and thinner subfoveal choroidal thickness ($P < 0.001$). One may infer that axial elongation associated rotation of the optic disc around the vertical axis with a posterior movement of the temporal disc margin may stretch and elongate the temporal peripapillary scleral flange. Because the length of the macular Bruch’s membrane did not markedly increase with longer axial length, as shown in a previous study, one may conclude that, in axially elongated eyes, the enlarged peripapillary scleral flange is no longer covered by Bruch’s membrane, so that a Bruch’s membrane-free region at the temporal disc border develops. That region fulfills the criteria for the parapapillary gamma zone.

The findings of our study agree with the results obtained in previous investigations on the association between longer axial length and width of gamma zone. In a study by Chui et al. on 72 healthy adults, the distance between the fovea and the temporal optic disc border and the distance between the temporal disc border and end of the peripapillary crescent (similar to gamma zone in our study) increased significantly with longer axial length. As a corollary, the distance between the fovea and the start of the crescent (similar to macular Bruch’s membrane length in our study) was only marginally associated with axial length. In the investigation of Chui et al., an increase in axial length by 10% was associated with an increase in the fovea–temporal disc border distance by 13%, whereas the outer neural retina expanded only by 4%. Examining 61 highly myopic (≥-6 D) eyes without myopic retinopathy, Nonaka et al. reported that the width of a gamma zone–like region increased with longer axial length. In a histomorphometric study, the length of the gamma zone was strongly associated with axial length. At a cutoff value of 26.5 mm in axial length, the size of the gamma zone showed a steep increase with longer axial length. Other studies reported the existence of a parapapillary zone free of Bruch’s membrane. Using the Fourier domain OCT, Park et al. examined the microstructural anatomy of the parapapillary region and reported that the edge of Bruch’s membrane did not extend to the optic disc margin in all eyes. Hayashi et al. assessed the peripapillary region in 100 patients with primary open-angle glaucoma and in 100 normal subjects and detected that, in 79 eyes, Bruch’s membrane was lacking at the temporal disc border. Lee et al. reported on slope-like and step-like configurations of the scleral bed and hump- and wedge-shaped appearances of Bruch’s membrane in the peripapillary region. These features were associated with longer axial length and resembled the gamma zone in our study.

The new finding in our study was that a wider parapapillary gamma zone was significantly associated with the amount of vertical optic disc rotation. If the optic disc rotates around the vertical axis, the temporal disc border moves backward while the superior disc pole and the inferior disc pole remain mostly unchanged in their relative position. The vertical disc rotation leads to a notable shortening of the image of the horizontal disc diameter and to an underestimation of the horizontal disc diameter when measured on two-dimensional fundus photographs. More importantly, the backward movement of the temporal disc margin will stretch the tissue at the temporal disc border, which is the temporal peripapillary scleral flange. It may cause an elongation of the peripapillary scleral flange, fitting with results of histomorphometric studies in which the peripapillary scleral flange in highly myopic eyes compared with emmetropic eyes was up to 10 times longer (5 vs. 0.5 mm), whereas its thickness was reduced up to 10%...
and absence of major ocular diseases. Such as age, level of education, body stature, body mass index, associated with axial length, after adjusting for parameters such as axial length. The lack of an association between the axial length and macular Bruch's membrane defects was independent of the elongation of the disc–foveal distance as described in a previous study was due to the appearance or enlargement of the papillary gamma zone.1 This may make one infer that the distance between the retinal photoreceptors in the macular and foveal area was not markedly dependent on axial length as long as highly myopic eyes with secondary macular Bruch's membrane defects were excluded. Correspondingly, a recent multivariate analysis revealed that within non-highly myopic eyes, better correct vision acuity was not significantly associated with axial length, after adjusting for parameters such as age, level of education, body stature, body mass index, and absence of major ocular diseases.3

The associations between the gamma zone width and other parameters such as a higher degree of fundus tessellation, thinner subfoveal choroidal thickness, and longer horizontal optic disc diameter may be due to associations between these parameters and longer axial length.9,17 The association between wider gamma zone and more marked optic disc rotation around the horizontal axis (P = 0.02) may be explained by an association between vertical disc rotation and horizontal disc rotation. The correlation between a larger gamma zone and longer disc–foveal distance has previously been described in studies in which the elongation in the disc–foveal distance with longer axial length was mainly due to the development or enlargement of the gamma zone. As a corollary, the length of the macular Bruch's membrane was mostly independent of axial length.

Potential imitations of our study should be taken into account. First, our study had a minimum age limit of 50 years, so that the findings of our study cannot directly be transferred on younger individuals. Second, our study included Chinese individuals, and because ocular dimensions may differ between ethnicities, the measurements obtained in our study population may not directly be transferred onto other populations. Third, measurements obtained in 2008 individuals or 59.6% of the 3468 participants of the Beijing Eye Study 2011 were included in the present investigation. The participants, compared with the nonparticipants, were significantly younger and had a significantly shorter axial length, so that a selection artifact may have occurred. It was, however, not the goal of our study to report on the mean size of the gamma zone in a population but to assess relationships between the gamma zone and other ocular and general parameters, so that a potential selection bias may not have markedly influenced the results and conclusions of our study. Fourth, it has remained unclear whether Bruch's membrane as a multilayered structure of two collagenous layers, separated from each other by an elastic layer and packed between the basement membranes of the retinal pigment epithelium and of the choriocapillaris, remodels in eyes undergoing axial elongation and optic disc rotation. Addressing that question would have needed a study design of a longitudinal investigation. However, because our study was a cross-sectional investigation, any conclusion on longitudinal changes and effects were limited in their validity.

In conclusion, the parapapillary gamma zone was associated with an axial elongation–induced rotation of the optic disc mainly around the vertical axis, leading to a stretching of the peripapillary scleral flange. Because macular Bruch's membrane length was independent of axial elongation, it leaves the temporal parapapillary region with an uncovered Bruch's membrane.

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