Size and Shape of Bruch’s Membrane Opening in Relationship to Axial Length, Gamma Zone, and Macular Bruch’s Membrane Defects

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PURPOSE. To assess axial elongation-associated characteristics in Bruch’s membrane opening (BMO) as the inner optic nerve head lamella.

METHODS. Participants of the population-based Beijing Eye Study without glaucoma underwent optical coherence tomography for measurement of the BMO size and shape.

RESULTS. The study included 365 individuals (mean age, 61.0 ± 8.7 years; range, 50–88 years; axial length, 24.45 ± 1.99 mm; range, 21.32–30.88 mm). Larger horizontal (mean: 1.62 ± 0.28 mm) and vertical (mean: 1.74 ± 0.27 mm) BMO diameters were linearly associated with longer axial length beyond an axial length of 26.0 mm (horizontal diameter: \( P < 0.001 \); standardized regression coefficient \( \beta: 0.66 \); nonstandardized regression coefficient B: 0.22; 95% confidence interval (CI): 0.16, 0.27; vertical diameter: \( P < 0.001 \); \( \beta: 40; B: 0.12; 95\% CI: 0.06, 0.18 \)). In multivariable analysis, wider largest gamma zone was associated with larger intrapapillary Bruch’s membrane (BM) overhanging on the side opposite to the largest gamma zone (\( P = 0.006; \beta: 0.14; B: 0.35; 95\% CI: 0.10, 0.60 \)) and with longer horizontal BMO diameter (\( P < 0.001; \beta: 0.46; B: 0.59; 95\% CI: 0.46, 0.73 \)). The widest BM overhanging location (superior to nasal) was inversely correlated with the widest gamma zone location (inferior to temporal). Within the axial length group of ≥28.0 mm, eyes with macular BM defects had a less markedly increased BMO than those without macular BM defects (2.27 ± 0.18 vs. 2.71 ± 0.41 mm; \( P = 0.019 \)). The difference between horizontal BMO diameter minus horizontal gamma zone width decreased (\( P < 0.001 \)) with longer axial length.

CONCLUSIONS. Beyond 26.0 mm of axial length, horizontal and vertical BMO diameter increased by 0.21 mm (95% CI: 0.16, 0.27) and 0.12 mm (95% CI: 0.06, 0.18), respectively, for each millimeter of axial elongation. Gamma zone may develop due to an axial elongation–associated BMO enlargement (\( \beta: 0.46 \)) and, to a minor degree, a BMO shift in direction to the macula (\( \beta: 0.14 \)). A large gamma zone may be protective against myopic macular BM defects.

Keywords: Bruch’s membrane opening, axial length, myopia, parapapillary gamma zone, macular Bruch’s membrane defects, optical coherence tomography, optic nerve head, Beijing Eye Study

The optic nerve head canal consists anatomically of three layers: Bruch’s membrane opening (BMO), the choroidal layer, and the layer of the peripapillary scleral flange, which is covered by the lamina cribrosa. The peripapillary scleral flange serves as the biomechanical anchor of the lamina cribrosa to the sclera and is separated from the lamina cribrosa by the intertwined peripapillary border tissue of Elschnig.1–8 The choroidal lamella is separated from the intrapapillary compartment by the peripapillary border tissue of Jacoby, which ends at Bruch’s membrane (BM). The Jacoby tissue continues into the Elschnig tissue and further on into the optic nerve pia mater.9–12 These changes include an enlargement of the optic disc, the borders of which were defined by the peripapillary border tissues; a rotation of the optic disc mostly around its vertical axis; and the development of parapapillary gamma zone as BM-free parapapillary region, located mostly at the temporal optic disc side.13–21 The mechanism of the development of gamma zone and to which degree the BMO accompanies the myopic enlargement of the optic disc has remained unclear so far. We therefore conducted this study to measure the size and shape of the BMO and of the parapapillary gamma zone and to correlate the findings with axial length.

METHODS

The population-based Beijing Eye Study was carried out in the region of Greater Beijing and consisted of an urban part and a rural part. It was approved by the Medical Ethics Committee of
the Beijing Tongren Hospital, and all study participants gave their written informed consent. All procedures adhered to the tenets of the Declaration of Helsinki. Living in the study region and having an age of ≥50 years in the year 2011 were the only eligibility criteria for inclusion into the study. Out of 4405 eligible individuals, 3468 (78.8%) subjects (1963 [56.6%] women) participated with a mean age of 64.6 ± 9.8 years (range: 50–93 years). There were 1633 (47.1%) individuals (943 [57.7%] women) coming from the rural region, with the remaining 1835 (52.9%) study participants (1020 [55.6%] women) living in the urban region. The study population and the study design have been described in detail previously.22

We included in the present investigation all right eyes that were examined in the Beijing Eye Study and that had an axial length ≥25.0 mm, and we randomly selected 200 right eyes out of the Beijing Eye Study population with an axial length of <25.0 mm and with a refractive error within ±1 diopters. Exclusion criteria were the presence of glaucomatous optic neuropathy, since the glaucomatous process might have changed the configuration of the optic nerve head, and BMO edges that could not clearly be delineated. Glaucoma was defined according to the optic nerve head criteria of the International Society of Geographic and Epidemiological Ophthalmology.52–54 Particularly in the highly myopic eyes, glaucoma was defined by an abnormal shape of the neuroretinal rim, such as pronounced neuroretinal rim notches in the inferior or superior disc region; an almost complete loss of neuroretinal rim in the inferior or superior disc region; or in a more advanced stage of glaucomatous optic neuropathy, an extension of the optic cup to the optic disc border (corresponding to an almost loss of neuroretinal rim) in a large sector or the whole region of the optic nerve head.

The optic nerve head, including the peripapillary area, was imaged by spectral-domain optical coherence tomography (OCT) (enhanced depth-imaging mode) (Spectralis; Heidelberg Engineering Co., Heidelberg, Germany). The technique has already been described previously.55–59 The optic disc scan protocol included six radial scan lines with a scan length of 6 mm, centered on the optic disc, and each comprising 100 A-scans. The parapapillary region was examined with the intrinsic viewer (Heidelberg Eye Explorer software version 1.7.0.0; Heidelberg Engineering), which automatically synchronized the vertical lines of each B-scan and the infrared image taken by the OCT device. In eyes in which the end of BM did not reach the optic disc border (defined by the peripapillary border tissue of Elschlag), the parapapillary gamma zone was defined as the region between the end of BM and the border of the optic disc (Fig. 1). We measured the horizontal diameter and vertical diameter of the BMO, with the measurement lines running through the optic disc center; the length of the part of BM overhanging into the intrapapillary compartment on the nasal optic disc side in the horizontal OCT section; the width of parapapillary gamma zone at the temporal optic disc side in the horizontal OCT sections; the largest gamma width and its location and the length of BM overhanging on the opposite side; and for eyes without gamma zone, the length of the largest BM overhanging and its location (Fig. 1). We calculated the effectively open part of the BMO as difference of BMO diameter minus gamma zone width. We additionally assessed the prevalence of macular BM defects as described previously.30 OCT images with a magnification of up to 200% were assessed by a trained examiner (QZ).

Using a commercially available statistical software package (SPSS for Windows, version 25.0; IBM-SPSS, Chicago, IL, USA), we first calculated the mean and standard deviations; medians and ranges of the main outcome parameters, that is, the diameters of the BMO; the length of the overhanging part of BM; and the width of gamma zone. In a second step, we performed a univariate analysis to assess associations between the main outcome parameters and other ocular and systemic parameters. In a third and final step, we carried out a multivariable analysis. We calculated the standardized regression coefficient β, the nonstandardized regression coefficient B, and the 95% confidence interval (CI). All P values were two-sided and considered statistically significant when they were <0.05.

RESULTS

The study included 365 individuals (162 [44.4%] men) (365 eyes). The individuals included in the present investigation as compared to the participants of the Beijing Eye Study, who were not included, were significantly younger (mean age: 61.0 ± 8.7 years [median: 58 years; range: 50–88 years] versus 65.0 ± 9.9 years; P < 0.001); had a significantly longer axial length (24.45 ± 1.99 mm [median: 24.14 mm; range: 21.32–30.88 mm] versus 23.10 ± 0.89 mm; P < 0.001); and did not differ significantly in gender (P = 0.69).

Mean horizontal BMO diameter was 1.62 ± 0.28 mm (median: 1.58 mm; range: 1.14–3.32 mm), and mean vertical BMO diameter was 1.74 ± 0.27 mm (median: 1.71 mm; range: 1.21–3.13 mm). In univariate analysis, longer horizontal and vertical BMO diameters were associated with longer axial length in a nonlinear manner (Figs. 2, 3). Up to an axial length of 26.0 mm, the association between horizontal BMO diameter was marginally significant (P = 0.02; β: 0.14), while the vertical BMO diameter was not significantly correlated with axial length (P = 0.06; β: 0.11). Beyond an axial length of 26.0 mm, both diameters were strongly and mostly linearly associated with longer axial length (horizontal BMO diameter: P < 0.001; β: 0.66; equation of the regression line: Horizontal BMO diameter [mm]: 0.21 [95% CI: 0.16, 0.27] × axial length [mm] –3.92; vertical BMO diameter: P < 0.001; β: 0.40; equation of the regression line: Vertical BMO diameter [mm]: 0.12 [95% CI: 0.06, 0.18] × axial length [mm] –1.50). Within the group of eyes with an axial length of ≤25.0 mm, the mean horizontal BMO diameter was 1.54 ± 0.17 mm, and the mean vertical BMO diameter was 1.67 ± 0.17 mm. If age was added as independent variable to the regression analysis, the BMO diameters were not significantly associated with age (all P > 0.15).

The mean ratio of the horizontal-to-vertical BMO diameter was 0.95 ± 0.12 (median: 0.95; range: 0.48–1.58). It increased with longer axial length (P = 0.001; β: 0.17) (Fig. 4).

The difference between the horizontal BMO diameter minus the horizontal gamma zone width was 1460 ± 220 μm (median: 1466 μm; range: 434–2008 μm). In the group of eyes with an axial length of ≤24.0 mm, it was statistically

FIGURE 1. OCT image of an optic nerve head. Yellow arrows: ends of BM; between left yellow arrow and black arrow: parapapillary gamma zone; yellow dots: undermining of BM at the nasal optic disc border.
independent of axial length ($P = 0.16; \beta: 0.10; B: 26; 95\% CI: -11, 63$). In the group of eyes with an axial length of more than 24.0 mm, it decreased significantly with longer axial length ($P = 0.001; \beta: -0.24; B: -47; 95\% CI: -75, -19$) ($P = 0.03; \beta: -0.25$) (Fig. 5).

The mean length of an overhanging BM into the intrapapillary compartment at the nasal optic disc side in the horizontal OCT sections was 263 ± 202 μm (median: 262 μm; range: 0–926 μm), and the length of an overhanging BM opposite the location of the widest gamma zone location was 363 ± 172 μm (median: 335 μm; range: 60–831 μm). The mean gamma zone width on the temporal disc side in the horizontal OCT section was 163 ± 328 μm (median: 0 μm; range: 0–2302 μm), and the mean gamma zone width at the location of its widest extension (in eyes with gamma zone) was 446 ± 425 μm (median: 297 μm; range: 58–2422 μm). The location of the widest intrapapillary overhanging of BM was between the 12 o’clock position and 3 o’clock position (for right eyes). The location of the widest gamma zone width was between the 6 o’clock position and 9 o’clock position (for right eyes).

In univariate analysis, the diameters of BMO, the length of the overhanging BM, and the width of gamma zone were significantly ($P < 0.005$) correlated with longer axial length. In multivariable regression analysis, a wider largest width of

**FIGURE 2.** Graph showing the distribution of the horizontal BM opening diameter in relationship to axial length in the Beijing Eye Study with a locally estimated scatterplot smoothing (LOESS), showing the difference in the relationship for eyes with an axial length of less than or more than 26.5 mm.

**FIGURE 3.** Graph showing the distribution of the vertical BMO diameter in relationship to axial length in the Beijing Eye Study with a locally weighted LOESS, showing the difference in the relationship for eyes with an axial length of less than or more than 26.5 mm.
gamma zone was associated with a longer horizontal BMO diameter ($P < 0.001$; $\beta$: 0.46; $B$: 0.59; 95% CI: 0.46, 0.73; variance inflation factor [VIF]: 1.37); a larger intrapapillary BM overhanging at the side opposite the largest gamma zone location ($P = 0.006$; $\beta$: 0.14; $B$: 0.35; 95% CI: 0.10, 0.60; VIF: 1.39); and longer axial length ($P < 0.001$; $\beta$: 0.42; $B$: 0.92; 95% CI: 0.67, 1.17; VIF: 1.76) (Fig. 6).

Macular BM defects were detected in five eyes with a mean age of 65.6 ± 11.2 years (range: 53.0–78.0 years) and a mean axial length of 29.4 ± 0.6 mm (range: 28.9–30.4 mm). In multivariable regression analysis, a longer horizontal BMO diameter was associated with a higher prevalence of macular BM defects as part of a myopic maculopathy ($P = 0.02$; $\beta$: 0.12; $B$: 283; 95% CI: 56, 509) after adjusting for longer axial length ($P < 0.001$; $\beta$: 0.49; $B$: 0.75; 95% CI: 60, 89) (Fig. 7). Within the group of eyes with an axial length ≥28.0 mm, the eyes with a macular BM defect had a significantly smaller BMO than did those without macular BM defects (2.27 ± 0.18 mm versus 2.71 ± 0.41 mm; $P = 0.019$) (Fig. 7).

**DISCUSSION**

In this population-based study, randomly selected non–highly myopic eyes with an axial length of less than 25.0 mm had a
mean horizontal and vertical diameter of the BMO of 1.54 ± 0.17 mm and 1.67 ± 0.17 mm, respectively. Beyond an axial length of 26.0 mm, both diameters increased (P > 0.001) linearly with axial length (Figs. 2, 3). The axial elongation-associated increase was slightly more marked for the horizontal diameter than for the vertical diameter, as indicated by an increase in the ratio of horizontal-to-vertical BMO diameter with longer axial length (Fig. 4). The horizontal BMO diameter minus the horizontal gamma zone width represented the effective opening of BM for the passage of the retinal nerve fibers and retinal vessels. Its mean horizontal diameter decreased with longer axial length in the group of eyes with an axial length of more than 24.0 mm (Fig. 5). An overhanging of BM into the intrapapillary compartment was observed mainly in the region from the superior to the nasal optic disc pole. The mean length of the overhanging BM of 263 ± 202 μm was significantly correlated with the mean width of parapapillary gamma zone in the location opposite the overhanging BM. As a corollary, the location of the widest intrapapillary BM overhanging was spatially correlated with the location of the widest gamma zone. The largest width of gamma zone was more strongly associated with a longer

**Figure 6.** Scattergram showing the distribution of the length of the intrapapillary BM overhanging at the location of the widest parapapillary gamma zone in relationship to the maximal gamma zone width in the Beijing Eye Study (r²: 0.29).

**Figure 7.** Graph showing the distribution of the horizontal BMO diameter stratified by axial length and the presence of macular BM defects in the Beijing Eye Study.
The BMO diameter increased in the present study with longer axial length in a nonlinear manner. There was only a slight enlargement of the BMO with longer axial length in eyes with an axial length of ≤26.0 mm and a relatively steep and linear increase in eyes with an axial length of >26.0 mm (Figs. 2, 3). Beyond an axial length of 26.0 mm, the horizontal BMO diameter increased by 0.21 mm (95% CI: 0.16, 0.27) and the vertical BMO diameter by 0.12 mm (95% CI: 0.06, 0.18) for each millimeter of axial elongation. Similar observations were made for the relationship between axial length and optic disc size as measured two-dimensionally upon ophthalmoscopy using optic disc photography.\textsuperscript{15,33} In these clinical studies, the optic disc size as measured ophthalmoscopically and the size of parapapillary gamma zone started to increase with longer axial length at a cutoff point of approximately 26.0 to 26.5 mm of axial length as examined in the present study, if the BMO diameters are calculated for the area calculation of an ellipse. The BMO area for eyes of Japanese subjects and measured a mean BMO area of 2.06 ± 0.45 mm\textsuperscript{2}. That area of 2.06 mm\textsuperscript{2} is quite similar to a BMO area of 2.02 mm\textsuperscript{2} for eyes with an axial length of <25.0 mm as examined in the present study, if the BMO diameters are taken for the area calculation of an ellipse. The BMO area for the whole population of the present study was 2.21 mm\textsuperscript{2}. The difference of the value of 2.02 mm\textsuperscript{2} as found for the nonmyopic eyes in our study population was due to the association between larger BMO diameters and longer axial length (Figs. 2, 3). A similar observation was reported by Nakanishi and colleagues.\textsuperscript{32}

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The etiology of the parapapillary gamma zone defined as the parapapillary region, and thus the BMO, it would lead to a circular gamma zone. A second mechanism for the development of gamma zone, in particular at the temporal disc border, may be a shift of the BMO in the direction of the macula. Considering the optic nerve head as a three-layered canal, a temporal shift of the BMO, leaving the choroidal opening and scleral opening behind, would lead to an overhanging of BM into the intrapapillary compartment at the nasal optic disc side and to a lack of BM on the temporal side. Findings in favor of this hypothesis were that the BM overhanging into the intrapapillary compartment was found mostly in the superior to nasal region, that the location of gamma zone was detected mostly in the inferior and temporal region, and that the length of the overhanging BM correlated with the width of gamma zone at the location opposite the overhanging BM (Fig. 6).\textsuperscript{56,57} Recently, an overhanging of BM and theoblunghess of the optic nerve fiber exit in myopic optic nerve heads has also been described and analyzed by Sawada and colleagues.\textsuperscript{57} While the hypothesis of a temporal BM shift has remained unproven as yet, the questions may arise regarding by which mechanism the BMO may be shifted or pushed in the direction of the macula. Recent histomorphometric investigations and experimental studies have suggested that during the process of myopic axial elongation, BM may get elongated or enlarged in the equatorial and retroequatorial region, and thus the BMO is pushed backward.\textsuperscript{58} The underlying choroid and sclera may only passively follow; consequently, the three-layered optic nerve head canal gets an oblique orientation, with a (paradox) course of the retinal nerve fibers running from the macula through the optic nerve head canal in anterior direction before bending backward in the direction of the nasal superior region of the orbit. It is interesting that a higher prevalence of macular BM defects was associated with a less markedly increased horizontal BMO diameter within the highly myopic group of eyes with an axial length of ≥28.0 mm (Fig. 7). Macular BM defects have recently been described as a hallmark of myopic maculopathy.\textsuperscript{59} Although the present study has only a cross-sectional design, Figure 7 also suggests that the axial elongation was associated first with an enlargement of the BMO, followed by the development of macular BM defects. One may speculate that the process of myopic axial elongation with an enlargement of the posterior half of the globe leads to an increased strain within BM, so first the physiological hole in the BM, that is, the BMO, enlarges before additional defects in the BM, followed by the development of macular BM defects. This notion fits with the observation that within the subgroup of highly myopic eyes, eyes with a macular BM defect as compared to eyes without macular BM defects had a smaller BMO (Fig. 7). It agrees with the findings made in a cross-sectional hospital-based study on highly myopic eyes in which the number of macular BM defects increased after an increase in the size of parapapillary gamma and delta zone.\textsuperscript{60} It also fits with findings that BM at the posterior pole neither elongates nor gets thinner in axially elongated eyes, that it is not elastic, and that it has a relatively high biomechanical strength.\textsuperscript{41,42}
group. We therefore presented the measurements of the BMO diameters separately for the non-highly myopic subgroup. Second, it can be difficult to delineate the end of BM on the OCT images in eyes with the gamma zone, so this inaccuracy might have increased the noise of the measurements. Despite such a noise, however, the associations were statistically significant; thus, this potential limitation may serve to strengthen the conclusions drawn. Third, in a similar manner, the determination of the length of the overhanging BM into the intrapapillary compartment can be difficult in some eyes since the overlying tissue may prevent a clear visualization. Fourth, the study population included only five eyes with macular BM defects. Although the difference in BMO size between the highly myopic eyes without macular BM defects versus those with macular BM defects was statistically significant ($P = 0.02$), the small number of eyes with macular BM defects may not allow a firm conclusion of, but may only hint at, such a correlation of larger BMO size and lower number of macular BM defects (Fig. 7). Fifth, an inclusion criterion of our study was the detectability of the BMO edges, thus eyes with indiscernible BMO edges were excluded.43 It may therefore remain unclear whether the results of our study can also fully explain the defects in highly myopic eyes.

References

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