Change of β-Zone Parapapillary Atrophy During Axial Elongation: Boramae Myopia Cohort Study Report 3

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PURPOSE. To investigate changes of β-zone parapapillary atrophy (PPA) during axial elongation.

METHODS. Change of β-zone PPA was evaluated by spectral-domain optical coherence tomography (SD-OCT) in myopic children for 2 years, prospectively. Using the infrared images acquired by a fixed scan circle in the glaucoma progression analysis (GPA) mode, the retinal pigment epithelial opening (RPEO) and the clinical disc margin (CDM) were manually delineated. The area and position of β-zone PPA was calculated as the differences from those of the RPEO and CDM, respectively. The β-zone PPA was further differentiated into βBM PPA (β-zone PPA with Bruch’s membrane [BM]) and γ-zone PPA (β-zone PPA without BM). The change of β-zone PPA was compared between the first and final visits.

RESULTS. The area of β-zone PPA increased in 35 eyes (76%). This increase was associated with RPEO area increase and CDM area decrease. The center of β-zone PPA moved along the direction of vascular trunk dragging, but to a lesser extent. The β-zone PPA enlargement was correlated with the extent of vascular trunk dragging (P = 0.014). In all eyes with β-zone PPA increase, the γ-zone portion had increased. Even in childhood, βBM PPA existed next to their γ-zone PPA in 11 eyes (24%), including 4 eyes that showed increase of both γ-zone and βBM portion during axial elongation.

CONCLUSIONS. Enlargement of β-zone PPA during axial elongation was affected by the extent and direction of vascular trunk dragging, thus implicating disproportionate growth between the retina and sclera.

Keywords: parapapillary atrophy, myopic crescent, myopia, OCT, glaucoma

Parapapillary atrophy (PPA) is a funduscopic finding that is divided into (1) the peripheral β-zone characterized by irregular pigmentation and (2) the central β-zone distinguished by the visibility of large choroidal vessels and sclera due to the lack of retinal pigment epithelium (RPE).1,2 β-zone PPA is especially noted for its association with glaucoma; indeed, it is larger and found more frequently in glaucoma patients than in normal subjects.2,4 Moreover, the presence of β-zone PPA is associated with development5–7 or progression of glaucoma.8,9 Therefore, β-zone PPA might represent an optic disc that is more vulnerable to glaucomatous damage. Its pathophysiology impacting on vulnerability to glaucoma, however, is still unknown. Investigation of the development of β-zone PPA might provide clues to its specific association with such vulnerability.

With the advent of spectral-domain optical coherence tomography (SD-OCT), each retinal layer in a cross-sectional image of the optic nerve head (ONH) complex can be delineated. With SD-OCT, β-zone PPA is further classified according to the presence or absence of Bruch’s membrane (BM): βBM PPA (β-zone PPA with BM) and γ-zone PPA (β-zone PPA without BM).10,11 Further, each type of PPA is reported to have different characteristics: βBM PPA is associated with glaucoma, while γ-zone PPA is associated not with glaucoma but rather with myopia.10–12 Previous studies have suggested that βBM PPA can be a leftover of complete RPE atrophy with aging,13 while γ-zone PPA can develop as the stretching of sclera and border tissue.14,15 However, plenty of cases of β-zone PPA in young eyes have both βBM and γ-zone PPA,10,11,16 which suggests that βBM and γ-zone PPA might share an etiology. Therefore, it is imperative to evaluate βBM and γ-zone PPA as unrelated to the aging process and prospectively.

To our best knowledge, there has been no longitudinal study evaluating β-zone PPA development in young healthy subjects with growing eyes. The purpose of the present study, then, was to investigate the structural change of β-zone PPA with axial elongation.

METHODS

This study included myopic children who had undergone regular checkups for myopia between February 2013 and September 2014 at Seoul National University Boramae Medical Center and had subsequently been enrolled in the Boramae Myopia Cohort Study. It was approved by the Institutional Review Board of Seoul National University Boramae Medical Center and conformed to the Declaration of Helsinki. All of the subjects’ guardians provided written informed consent before enrollment.
The Boramae Myopia Cohort Study was undertaken to identify and elucidate structural changes occurring with axial elongation in eyes with progressive myopia. The inclusion criteria were myopic eyes (spherical equivalent of cycloplegic refraction test ≤−0.75 diopters [D]) in growing-age (7- to 12-year-old) children without any other ocular diseases. Enrollment was offered to all subjects meeting the inclusion criteria during the inclusion periods, and only those subjects whose legal guardians agreed to their participation were initially included. All subjects had full correction using eyeglasses and were not intervened to reduce myopia progression. With inclusion, each subject underwent a complete ophthalmic examination including best-corrected visual acuity (BCVA) assessment, cycloplegic refraction test, slit-lamp biomicroscopy, tonometry, dilated funduscopy examination, keratometry for corneal curvature measurement (RKI-7700; Nidek Co., Ltd., Hiroshi, Japan) and axial length measurement (IOLMaster version 5; Carl Zeiss Meditec, Inc., Dublin, CA, USA). For optic disc evaluation, fundus photography (TRC-NW8; Topcon Corp., Tokyo, Japan) and SD-OCT (Spectralis OCT; Heidelberg Engineering, Inc., Heidelberg, Germany) scans were performed. Using SD-OCT, circumpapillary retinal nerve fiber layer (RNFL) thickness measurement was performed in the glaucoma progression analysis (GPA) mode and enhanced-depth imaging (EDI) scanning was done to capture cross-sectional images of the deep ONH complex. Details on the scan protocol follow.

The exclusion criteria were eyes with a BCVA of less than 20/30, history or evidence of significant ocular disease, including congenital optic disc anomaly or any kind of ocular surgery, a good quality image (i.e., quality score >15) could not be obtained for more than 5 sections of EDI SD-OCT disc scans (when the quality score does not reach 15, the image-acquisition process automatically stops and images of the respective sections are not obtained) and less than 4 visits during the study period. Both eyes were examined for the analysis.

**Measurement of β-Zone PPA Changes**

In the GPA mode, the scan circle for circumpapillary RNFL measurement could be traced through all examination periods. To compare the changes between the first and final visits, the confocal infrared fundus images obtained in the GPA mode, as previously described, were aligned and transposed by commercial software (Photoshop; Adobe Systems, Inc., San Jose, CA, USA) using the circle scan and foveo-disc axis as references. With the en-face view of infrared fundus images, we analyzed the changes of β-zone PPA area and position with axial elongation.

To measure the β-zone PPA area, two boundaries were drawn in infrared fundus images: the retinal pigment epithelium opening (RPEO, which is the area without the RPE) and the clinical disc margin (CDM). The infrared images were enhanced using the “find edges” function in the ImageJ software (version 1.51; National Institute of Health, Bethesda, MD, USA), and the demarcation lines of the RPEO and CDM were drawn manually by one observer (KML; Supplementary Figs. S1A–D). Using the ImageJ program, the areas of the RPEO and CDM were measured, and the difference between them was defined as the area of β-zone PPA (Fig. 1). Changes of β-zone PPA area subsequently were compared between the first and final visits.

The change of β-zone PPA center was defined as a vector between the centers of β-zone PPA at the initial and final visits (Fig. 2A). The centers of the RPEO and CDM were calculated using the ImageJ program. Since we knew the areas and centers of the RPEO and CDM, we could calculate the center of β-zone PPA for each visit (Supplementary Fig. S1E). For comparison, the positional change of the central retinal vascular trunk was defined as vascular trunk dragging (d; Fig. 1). The vectors indicating the changes of β-zone PPA center and vascular trunk were compared with each other. Data on the left eyes were flipped to the right-eye orientation.

**Determination of β-Zone PPA Change**

First, serial transposed infra-red images with manually delineated PPA margin (Fig. 1) were independently assessed by two independent observers (KML and MK). Each observer, who was masked to the subject information, classified whether β-zone PPA had increased or not. Then, in the eyes with β-zone PPA increase, the same observers determined, using the infrared images with delineation, which part of the β-zone PPA (the γ-zone or βHM or both) had increased (Figs. 1D, 1E, Supplementary Fig. S2). In our study cohort, no eye had an isolated increase of βHM without an increase of γ-zone PPA. Therefore, the types of PPA changes were further classified into (1) the no increase of PPA group, (2) the γ-zone PPA increase group, and (3) the βHM γ-zone PPA increase group. In cases of disagreement, a third observer (SHK) was consulted to achieve consensus.

**Data Analysis**

The group comparisons were performed by Kruskal-Wallis test. The correlations between the differences of the measured values at the first and final visits were analyzed by Spearman’s correlation coefficient. The generalized estimating equation (GEE) regression model was applied to determine the factors associated with β-zone PPA enlargement while accounting for the correlation of paired eyes from the same subject. Univariate
and multivariate GEE analyses were used to determine the factors associated with the increase of β-zone PPA area. Parameters with a \( P \) value < 0.05 in the univariate analysis were included in the subsequent multivariate analysis.

The threshold for statistical significance was set at \( P < 0.05 \). Statistical tests were performed with commercially available software (Stata version 14.0; StataCorp LLC, College Station, TX, USA) and R statistical packages version 3.3.3 (available in the public domain, http://www.R-project.org). Except where otherwise indicated, the data are presented as mean ± standard deviation values.

**RESULTS**

Thirty-one subjects were initially enrolled in this cohort study. Among them, 3 declined to participate in the study and 5 were dropped due to noncooperation with the study protocol. These exclusions resulted in a final study population of 46 eyes of 23 subjects. The study subjects were aged 9.6 ± 1.7 years (range, 6.7–12.5 years) and included 9 boys and 14 girls. At baseline, the average IOP was 15.1 ± 2.5 mm Hg, the refractive error -4.26 ± 2.34 D, and the axial length 24.80 ± 1.28 mm; β-zone PPA was observed in 36 eyes. On the final visit, 42 eyes had β-zone PPA, and eyes with β-zone PPA had more myopic
refractive error, longer axial length, and larger BMO than those without \( \beta \)-zone PPA (Table 1). Among the eyes with \( \beta \)-zone PPA, those with \( \beta_{BM} \) \( \gamma \)-zone PPA had longer axial length and larger PPA than did those with only \( \gamma \)-zone PPA.

On the final visit, the areas of RPEO had increased by 0.224 \( \pm 0.310 \) \( \text{mm}^2 \), while those of CDM decreased by 0.135 \( \pm 0.214 \) \( \text{mm}^2 \), resulting in the increase of \( \beta \)-zone PPA by 0.359 \( \pm 0.400 \) \( \text{mm}^2 \) (Fig. 3). The increase of the \( \beta \)-zone PPA area was correlated with both increase of axial length (Spearman’s \( \rho = 0.527, P < 0.001 \); Fig. 4A) and extent of vascular trunk dragging (Spearman’s \( \rho = 0.514, P < 0.001 \); Fig. 4B). In the GEE analysis on all eyes, the increase of \( \beta \)-zone PPA was correlated with dragging of vascular trunk (\( P = 0.014 \)) and, to marginal significance, with axial length growth (\( P = 0.056 \); Table 2). The center of \( \beta \)-zone PPA had moved in the same direction of vascular trunk dragging, though to a lesser extent (Fig. 2B, red arrows).

The change of \( \beta \)-zone PPA composition is plotted in Figure 5. As for the \( \beta \)-zone PPA subtypes, at baseline, 25 eyes had only \( \gamma \)-zone PPA, while 11 had \( \beta_{BM} \) \( \gamma \)-zone PPA. In all cases, \( \beta \)-zone PPA appeared as a single crescent with an adjacent oval optic disc, and the inner margin of the BM could not be determined by fundus photography (Figs. 1B1, 1F). Eleven eyes (4 eyes without PPA, 5 with \( \gamma \)-zone PPA, and 2 with \( \beta_{BM} \) \( \gamma \)-zone PPA) did not show PPA changes. In the other 35 eyes with \( \beta \)-zone PPA change, \( \gamma \)-zone PPA had increased in all cases: 6 eyes did not have PPA initially and acquired \( \gamma \)-zone PPA, 20 eyes experienced the increase of preexisting \( \gamma \)-zone PPA (Fig. 6), and 5 eyes with preexisting \( \beta_{BM} \) \( \gamma \)-zone PPA showed an increase of \( \gamma \)-zone PPA (Fig. 7). The increase of \( \gamma \)-zone PPA area was associated with CDM area decrease, along with vascular trunk dragging in the opposite direction (Figs. 6, 7).

In 4 eyes (36%) with preexisting \( \beta_{BM} \) \( \gamma \)-zone PPA, both parts—\( \beta_{BM} \) and \( \gamma \)-zone PPA—increased during axial elongation (Table 3, Group C2; Fig. 8). The funduscopic distance between the fovea and the temporal margin of \( \beta \)-zone PPA had decreased with axial elongation in all cases (Figs. 8C, 8F). The eyes with \( \beta_{BM} \) \( \gamma \)-zone PPA increase shared two common

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**Table 1. Demographic Profiles of Eyes According to \( \beta \)-Zone Parapapillary Atrophy at Final Visit**

<table>
<thead>
<tr>
<th></th>
<th>Group A No PPA (n = 4)</th>
<th>Group B ( \gamma )-Zone PPA (n = 31)</th>
<th>Group C ( \beta_{BM} ) ( \gamma )-Zone PPA (n = 11)</th>
<th>( P )</th>
<th>Post Hoc Test</th>
</tr>
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<tbody>
<tr>
<td>Final age, y</td>
<td>11.5 ± 2.0</td>
<td>11.8 ± 1.6</td>
<td>12.1 ± 1.3</td>
<td>0.985*</td>
<td>A &gt; B = C</td>
</tr>
<tr>
<td>Final spherical equivalent, D</td>
<td>–2.75 ± 0.71</td>
<td>–5.85 ± 2.21</td>
<td>–6.56 ± 2.54</td>
<td>0.014*</td>
<td>A &gt; B = C</td>
</tr>
<tr>
<td>Average IOP, mm Hg</td>
<td>15.1 ± 5.1</td>
<td>15.4 ± 2.3</td>
<td>15.3 ± 2.9</td>
<td>0.995*</td>
<td></td>
</tr>
<tr>
<td>Final corneal curvature, D</td>
<td>46.03 ± 2.56</td>
<td>45.56 ± 1.22</td>
<td>43.40 ± 1.54</td>
<td>0.092*</td>
<td></td>
</tr>
<tr>
<td>Final axial length, mm</td>
<td>22.90 ± 1.78</td>
<td>25.54 ± 0.93</td>
<td>26.21 ± 1.02</td>
<td>0.003*</td>
<td>A &lt; B &lt; C</td>
</tr>
<tr>
<td>( \Delta ) Axial length, mm</td>
<td>370 ± 264</td>
<td>680 ± 398</td>
<td>731 ± 355</td>
<td>0.277*</td>
<td></td>
</tr>
<tr>
<td>( \Delta ) Border length, ( \mu ) m</td>
<td>0</td>
<td>88 ± 122</td>
<td>153 ± 166</td>
<td>0.145*</td>
<td></td>
</tr>
<tr>
<td>Final BMO diameter, ( \mu ) m</td>
<td>1483 ± 108</td>
<td>1957 ± 285</td>
<td>2015 ± 294</td>
<td>0.005*</td>
<td>A &lt; B = C</td>
</tr>
<tr>
<td>Final PPA area, ( \mu ) m²</td>
<td>0</td>
<td>1.20 ± 1.02</td>
<td>2.11 ± 1.12</td>
<td>0.001*</td>
<td>A &lt; B &lt; C</td>
</tr>
<tr>
<td>( \Delta ) PPA area, ( \mu ) m²</td>
<td>0</td>
<td>0.29 ± 0.26</td>
<td>0.69 ± 0.57</td>
<td>0.001*</td>
<td>A &lt; B &lt; C</td>
</tr>
<tr>
<td>PPA change</td>
<td>0</td>
<td>20 (65%)</td>
<td>9 (82%)</td>
<td>0.014†</td>
<td></td>
</tr>
</tbody>
</table>

\( \beta \)-zone PPA; \( \beta_{BM} \)-zone PPA with Bruch’s membrane (BM); D, diopters; IOP, intraocular pressure; BMO, BM opening.

* Comparison performed using Kruskal-Wallis test with post hoc Conover-Iman test to compare differences among three groups.

† Comparison performed using chi-square test.

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**FIGURE 2.** Change of \( \beta \)-zone PPA during axial elongation. (A) \( \beta \)-zone PPA could be defined as the exclusion of the CDM from the RPEO. With axial elongation, both RPEO and CDM changes induced \( \beta \)-zone PPA change (dashed lines, initial margin; solid lines, final margin). Using the centers and areas of the RPEO and CDM, we could calculate the center of \( \beta \)-zone PPA on each visit (see Supplementary Fig. S1E). Change of \( \beta \)-zone PPA center was defined as a vector (red arrow) for comparison with vascular trunk dragging (Fig. 1, d). (B) Comparison of shift between \( \beta \)-zone PPA (red arrows) and vascular trunk (gray arrows). Data on the left eyes are flipped to the right-eye orientation. (B1) Eyes with inferior vascular trunk dragging, (B2) Eyes with inferior vascular trunk dragging. Please note that to define \( \beta \)-zone PPA change as a vector, only cases having \( \beta \)-zone PPA at their initial visits were included in this analysis. The shift of the \( \beta \)-zone PPA center in the same direction as that of vascular trunk dragging, and the extent of \( \beta \)-zone PPA center change is smaller than that of vascular trunk change.
features: (1) severe dragging of vascular trunk reaching the nasal disc margin (Fig. 8D) and (2) the increase of PPA area was most prominent among the groups (Table 3).

DISCUSSION

In our previous studies, central vascular trunk in the ONH was dragged nasally with lamina cribrosa (LC) shifting during axial elongation, while the position and the diameter of the BMO were preserved. In this study, β-zone PPA increased in the same direction of vascular trunk dragging. The extent of PPA enlargement was correlated with that of vascular trunk dragging. These results indicate that the development of β-zone PPA during axial elongation is the result of LC and sclera shifting beneath the preserved BMO. Additionally, we observed β- and γ-zone PPA and its expansion in childhood myopic eyes. To our knowledge, this is the first longitudinal study to investigate β-zone PPA-related change in association with axial elongation in myopic children.

β-zone PPA is a common funduscopic finding with a diverse origin. Certain types of β-zone PPA, such as γ-zone PPA, are reported to be associated with myopia. In this study, we

Table 2. Factors Associated With Increase of β-Zone Parapapillary Atrophy During Axial Elongation

<table>
<thead>
<tr>
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<th>Univariate Analysis</th>
<th>Multivariate Analysis*</th>
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<tr>
<td></td>
<td>Coefficient</td>
<td>95% CI</td>
</tr>
<tr>
<td>Baseline spherical equivalent, D</td>
<td>-24.715</td>
<td>(-79.695 to 30.265)</td>
</tr>
<tr>
<td>Average IOP, mm Hg</td>
<td>0.255</td>
<td>(-53.177 to 53.688)</td>
</tr>
<tr>
<td>Baseline corneal curvature, D</td>
<td>-27.908</td>
<td>(-120.362 to 64.546)</td>
</tr>
<tr>
<td>Δ Axial length, μm</td>
<td>0.541</td>
<td>(0.249 to 0.834)</td>
</tr>
<tr>
<td>Δ Border length, μm</td>
<td>0.648</td>
<td>(-0.154 to 1.450)</td>
</tr>
<tr>
<td>Dragging of vascular trunk, μm</td>
<td>1.727</td>
<td>(0.888 to 2.566)</td>
</tr>
</tbody>
</table>

Univariate and multivariate analyses were performed using the generalized estimating equation (GEE) regression model. Statistically significant values (P < 0.05) are shown in bold. PPA, parapapillary atrophy; CI, confidence interval; D, dioptries; IOP, intraocular pressure.

* Variables with P < 0.05 in the univariate analysis were included in the subsequent multivariate analysis.
recorded an increase of β-zone PPA in 35 eyes (76%) during axial elongation, with the most prominent change occurring in the γ-zone. The increase of γ-zone PPA represented scleral overgrowth relative to the inner retinal structures in the growing eye. This might explain why γ-zone PPA is associated with myopia.\textsuperscript{10,11} This speculation is in line with Chui et al.\textsuperscript{19} Having calculated the expansion of each layer according to the axial length, they concluded that retinal stretching might not mirror scleral growth, thus resulting in slippage of the sclera to the retina during eye growth. Therefore, γ-zone PPA is a sign of disproportionate growth between layers during axial elongation.

In the Beijing Eye Study, the association of axial length, γ-zone PPA, and optic disc rotation was reported.\textsuperscript{20} Those authors stated that γ-zone PPA was associated with axial elongation-induced rotation of the optic disc leading to stretching of the temporal peripapillary scleral flange.\textsuperscript{20} However, we doubt any supposed cause of optic disc rotation, as it is difficult to imagine any other force exerted on the optic disc during axial elongation. Instead, we have speculated that this association reflects the oblique-directional outer-wall expansion with growth. As shown in Figure 6, oblique elongation of γ-zone PPA and subsequent change of the optic disc margin would give the false impression that the optic disc had rotated. Upon closer inspection, in fact, the peripapillary vessels and RPEO were not rotated—only the CDM was shifted in the superonasal direction. This suggested that the alleged torsion or rotation of the optic disc could also be understood as a fundoscopic presentation of outer-wall (LC and sclera) expansion through the fixed window of the BMO.

Higher prevalence of glaucoma may be associated with a defective layered architecture in the β-zone PPA. Disturbed ONH blood/retinal barrier adjacent to β-zone PPA might facilitate diffusion of noxious molecules.\textsuperscript{21} In this study, however, we present another source of ONH vulnerability to glaucomatous damage in the β-zone PPA: the LC shift. With axial elongation, the growth of the sclera overwhelms the growth of the retina,\textsuperscript{14} and scleral overgrowth would result in LC shifting.\textsuperscript{15} Therefore, the presence of β-zone PPA would implicate the tensile stress exerted on the LC with expansion of the outer-load bearing structures in the course of eyeball growth.

Interestingly, we could observe the βBM PPA and its expansion even in the subjects’ first decade. βBM γ-zone PPA
accounted for 26% of β-zone PPA, and both $\beta_{BM}$ and γ-zone PPA increased in a third of $\beta_{BM}$ γ-zone PPA during axial elongation. We could not imagine that those eyes had undergone ischemic or senile changes, as the subjects were all healthy young children. The implication here was that $\beta_{BM}$ PPA, as well as γ-zone PPA, were enlarged during axial elongation. We speculated that increased $\beta_{BM}$ PPA was due to tensile strain on the eyeball since all of the subject eyes had vascular trunks located adjacent to the nasal margin of the RPEO at the patients’ final visits. The final position of the vascular trunk might reflect severe expansion that the eye had to endure. Mechanical stretching could have increased the $\beta_{BM}$ PPA by several mechanisms. First, the RPE could migrate over the BM during IOP elevation. Wang and colleagues speculated that the RPEO can slide over the BM in eyes lacking any firm attachment between the RPE and the BM. Tensile strain associated with eyeball growth might induce similar migration along with enlargement of the RPEO void area within

| Table 3. Characteristics of Eyes With Increased β-Zone Parapapillary Atrophy |
|----------------------|----------------------|----------------------|----------------------|----------------------|
|                      | Increased Portion of β-Zone PPA |
|                      | $\beta_{BM}$ γ-Zone PPA (n = 20) | $\beta_{BM}$ γ-Zone PPA (n = 5) | $\beta_{BM}$ γ-Zone PPA (n = 4) | $P^*$ Post Hoc Test |
| Baseline age, y      | 8.8 ± 1.4              | 9.5 ± 1.4              | 9.1 ± 0.3              | 0.254 B1 < C2         |
| Baseline spherical equivalent, D | −3.98 ± 2.40          | −3.88 ± 2.67            | −6.53 ± 1.63           | 0.202 B1 < C2         |
| Average IOP, mm Hg   | 15.1 ± 2.5             | 14.7 ± 2.7              | 15.5 ± 4.1             | 0.925 B1 < C2         |
| Baseline corneal curvature, D | 43.58 ± 1.17           | 43.00 ± 1.41            | 44.47 ± 1.55           | 0.324 B1 < C2         |
| Δ Axial length, μm   | 855 ± 539              | 692 ± 382              | 1005 ± 157             | 0.251 B1 < C2         |
| Δ Border length, μm   | 108 ± 117              | 208 ± 211              | 176 ± 69               | 0.458 B1 < C2         |
| Dragging of vascular trunk, μm | 176 ± 122              | 133 ± 27               | 261 ± 142              | 0.244 B1 < C2         |
| Δ RPEO area, mm²      | 0.152 ± 0.155          | 0.312 ± 0.097           | 1.088 ± 0.360          | 0.001 B1 < C1 < C2   |
| Δ CDM area, mm²      | −0.248 ± 0.216         | −0.131 ± 0.231          | −0.230 ± 0.205         | 0.684 B1 = C1 < C2   |
| Δ PPA area, mm²      | 0.400 ± 0.262          | 0.443 ± 0.182           | 1.318 ± 0.374          | 0.006 B1 = C1 < C2   |

PPA, parapapillary atrophy; $\beta_{BM}$, β-zone PPA with Bruch’s membrane (BM); D, diopters; IOP, intraocular pressure; RPEO, retinal pigment epithelial opening; CDM, clinical disc margin.

* Comparison performed using Kruskal-Wallis test with post hoc Conover-Iman test to compare the differences among the three groups.
**FIGURE 7.** Sample case with $\beta_{BM}$ $\gamma$-zone PPA and increase of $\gamma$-zone. (A) Infrared fundus image of radial scans indicating BMO margin (red dots). (B, E) Fundus photographs. (C, F) Infrared fundus images with arrows indicating SD-OCT scans. (D, G) SD-OCT images of initial (top row) and final (bottom row) visits. The horizontal green arrows indicate the horizontal green lines, which are indicative of the termination of the RPE. With axial elongation, $\gamma$-zone PPA (between yellow arrowheads and red arrows) increased, while the outer $\beta_{BM}$ PPA was preserved (between red arrows and green vertical lines).

**FIGURE 8.** Sample case with $\beta_{BM}$ $\gamma$-zone PPA and increase of both portions. (A–C) Initial visit. (D–F) Final visit. (A, D) Infrared fundus images. According to the scan circle reference, $\beta$-zone PPA was increased at the final visit. The red dots indicate the termination of the BM, as obtained by serial B-scan images (see Supplementary Fig. S2). These demarcation lines show the increase of both portions during axial elongation. The green arrows indicate where the B-scans were performed. (B, E) B-scan SD-OCT images (top) and schematic sketches (bottom). The red arrows indicate the termination of the BM, and the green lines indicate the termination of the RPEO, both of which were determined on infrared images (A, D: short vertical lines). The images within the inset are magnified for better visualization of the increase of the $\beta_{BM}$ portion. With axial elongation, both the $\gamma$-zone portion and the $\beta_{BM}$ portion have increased. In the schematic sketches, the growth of the sclera (gray lines) from the original position (dotted line) requires the posterior displacement of the retina and subsequent enlargement of the area to be covered by the RPE. The RPE density at the posterior pole from the fovea (expressed as blue lines), however, is preserved, and thereby, the end of the free BM (red lines) is stretched to the foveal side as the termination of the RPE (blue dots) moves toward the fovea. (C, F) Whole enface fundus images. The reference lines (dashed lines) are drawn along the fovea, and the centers of the circle scans are acquired in the GPA mode. It is clearly shown in the enface view that the distance between the center of the circle scan and the fovea has not changed. This contrasts with the shorter distance between the RPE termination (blue dots) and the fovea at the final visit. We speculated that posterior displacement of fovea might result in a shorter distance as measured on the enface plane (E, schematic sketch).
Parapapillary Atrophy During Axial Elongation

As for a second possible stretching mechanism, the BM can be stretched during axial elongation. Jonas et al. reported that RPE density in the posterior pole had no association with axial length, while RPE density in the equatorial region showed a negative correlation with axial length. This suggests that the posterior polar retinal structure is preserved during axial elongation. To achieve this, scleral growth might be compensated, initially, by an outer-wall shift. Further growth, however, requires a change in the retinal curvature, which would increase the distance to be covered by the RPE-BM complex (Figs. 8B, 8E). Since the RPE in the posterior pole would have only limited stretching capacity, an elastic membrane—the bare BM within β-zone PPA—would be stretched to compensate for this (Figs. 8, 9). The extent of BM stretching, calculated based on the second hypothesis, approximately corresponded to the measured extent of the β_BM PPA increase (Supplementary Fig. S5).

**Figure 9.** Schematic speculative summary of PPA changes. During the early developmental period, optic nerve head (ONH) formation requires delicate interactions of three different layers: the surface ectoderm (blue layer), the mesenchymal tissue (orange layer) and the neuroepithelium (yellow and green layers, top right). Invagination of the lens placode (surface ectoderm) separates the neuroepithelium into two parts: the neural retina (yellow layer) and the outer wall that forms the RPE layer (green layer). The mesenchymal tissue forms the sclera, LC and choroid, and covers the outer space (orange layer). Since the neural retina is connected to the brain, the future RPE layer and mesenchymal layer should incorporate into the neural retina to over the entire posterior surface (top left). Most eyes have sound attachment between the RPE and the BM, which is the outer membrane of the RPE layer. In some eyes, however, the BM, which is also the outer membrane of the choroid, could exist without the RPE, owing to alignment failure or RPE maintenance failure. This defective closure would be exaggerated during axial growth. The observable features in our study are drawn within the green box. In most eyes with firm attachment between the RPE and BM, γ-zone PPA appears and the RPEO equals the BMO (see Fig. 6). Some eyes with defective closure, however, have β_BM γ-zone PPA of the crescent shape (Fig. 1) in childhood. In this case, axial elongation leads mostly to the enlargement of γ-zone PPA (Fig. 7). In the case of severe dragging, however, eyeball growth requires the change of retinal curvature (gray lines, Fig. 8). This regional change will increase the distance to be covered by the RPE while it is more firmly attached at the foveal side than at the juxtapapillary side with pre-existing β_BM γ-zone PPA. As a result, an elastic membrane, BM within β-zone PPA, may increase to compensate for this.
Previously, $\beta_{BM}$ PPA was reported to be associated with older age, less myopia, and glaucoma.\textsuperscript{15-16} Although we tentatively agree, we wonder whether we could regard all $\beta_{BM}$ PPA cases as the same. We observed enlargement of $\beta_{BM}$ PPA in healthy children; $\beta_{BM}$ $\gamma$-zone PPA in our study; therefore, is clearly a different entity from $\beta_{BM}$ PPA in elderly individuals. Since $\beta_{BM}$ $\gamma$-zone PPA induced by expansion of sclera will definitely be of a different nature compared with $\beta_{BM}$ PPA of senile etiology, we should differentiate $\beta_{BM}$ PPA to investigate further the prognostic value of each subtype of $\beta$-zone PPA. Our study may provide a clue to such differentiation: severe vascular trunk shifting in eyes with $\beta_{BM}$ $\gamma$-zone PPA might suggest that PPA is induced by stretching.

It should be noted that $\beta_{BM}$ PPA did not appear de novo while some eyes acquired $\gamma$-zone PPA during our study period, which suggested that $\beta_{BM}$ PPA may appear during the earlier stages of development. At the optic disc, the embryonic fold of mesenchymal origin and that of neuroectodermal origin should meet (Fig. 9).\textsuperscript{24} To be specific, the BM is the outer membrane of the RPE (neuroectodermal origin) as well as the inner membrane of the choroid (mesenchymal origin). The BM without RPE ($\beta_{BM}$) could appear as a misalignment of those layers. Moreover, the maintenance of the RPE in the optic cup is regulated by signaling pathways through the neuroectoderm or mesenchyme.\textsuperscript{25} Failure of RPE maintenance, induced by inaccurate alignment, might also result in a BM devoid of the RPE.

Our study showed that such a misalignment could be widened by stretching with axial elongation. With axial elongation, the most prominent change occurs in the $\gamma$-zone because the attachment is weaker between the inner retinal structure and outer walls (LC and sclera) than it is between the RPE and BM. If the growth of the outer wall is too large to be compensated by shifting, however, the BM can be stretched and the RPE might slide, especially when the attachment between the RPE and BM is not sufficiently strong. This resulted in enlargement of the RPEO and $\beta_{BM}$ $\gamma$-zone PPA (Fig. 8). In the present study, the fact that eyes with $\beta_{BM}$ $\gamma$-zone PPA increase shared severe dragging of vascular trunk and large temporal PPA lent support to our speculation.

It should be noted that the change of $\beta$-zone PPA did not reflect the LC shift directly. The extent of LC shift was larger than that of $\beta$-zone PPA change. First, the rotation of the BT (from internally oblique to externally oblique) could compensate for LC shift.\textsuperscript{14} Second, the LC itself, as an elastic tissue, could be stretched in certain cases. In such eyes, the distance from the LC margin and the pore of the vascular trunk might increase rather than the PPA. Finally, PPA changes above the BMO ($\beta_{BM}$ PPA), in the direction counter to that of vascular trunk dragging, might conceal changes below the BMO (LC shift). These facts imply that outer-wall shift cannot be estimated solely based on $\beta$-zone PPA. Although the presence of $\beta$-zone PPA indicates a shift, the extent of $\beta$-zone PPA cannot be used as a marker of LC shift.

This study has several limitations. First, the enrollment was small. Since our institute is a secondary referral hospital, children without any ocular diseases except myopia are not common. In addition, there was no obvious benefit of participation commensurate with the time-consuming extra examinations that had to be performed every 6 months over a period of 2 years. In this situation, patient recruitment was somewhat difficult. Nevertheless, despite the small sample size, we obtained statistically significant findings regarding the factors correlated with increased $\beta$-zone PPA. Differences among the subgroups were also significant according to a nonparametric analysis that does not assume a normal distribution of data. Second, the study period was limited. For compliance, we could not image the ONH of the subjects prior to 6 years of age. In their earlier developmental stages, more dynamic changes would have occurred.\textsuperscript{29} Furthermore, it should be noted that the extent of $\beta$-zone PPA changes in our study would have been larger if we had observed the subjects longer. Therefore, our findings, as counterexamples to the widespread belief that $\beta$-zone PPA can be differentiated according to the presence or absence of BM,\textsuperscript{10-11} are meaningful since they could be found even within a limited examination period. Finally, we were not able to determine anything as to the prognostic value of $\beta$-zone PPA in our subjects. All the study subjects were healthy myopic children, and none of them had developed glaucoma. Although the dragging was more severe in eyes in the $\beta_{BM}$ $\gamma$-zone PPA increase group, we do not know whether this would increase the risk of glaucomatous optic neuropathy in those eyes.

In conclusion, $\beta$-zone PPA increased in the direction along to LC shift during axial elongation. Although $\beta$-zone PPA increased mostly in the $\gamma$-zone PPA, $\beta_{BM}$ $\gamma$-zone PPA also was found in the children and increased in their first decade. Presence or absence of BM cannot reveal anything specific as to the background of $\beta$-zone PPA development. $\beta_{BM}$ PPA adjacent to $\gamma$-zone PPA could be associated with axial elongation during childhood, when the vascular trunk is located in the direction opposite to the PPA. Further study investigating $\beta$-zone PPA with BM ($\beta_{BM}$ PPA), specifically in the etiological aspect, is warranted.

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