Cross-sectional Anatomic Configurations of Peripapillary Atrophy Evaluated with Spectral Domain-Optical Coherence Tomography

Kelvin Yoon Chiang Lee,1,2 Atsuo Tomidokoro,1 Rei Sakata,1 Shinsuke Konno,1 Chibiro Mayama,1 Hitomi Saito,1,3 Keiko Hayashi,1 Aiko Iwase,5 and Makoto Araie1

PURPOSE. To evaluate the cross-sectional configurations of peripapillary atrophy (PPA)-α and -β in ophthalmologically normal subjects using spectral domain-optical coherence tomography (SD-OCT).

METHODS. One hundred twenty normal subjects had a complete ophthalmic examination including axial length measurement, standard automated perimetry, fundus imaging with photography, and SD-OCT (3D OCT-1000; Topcon Inc., Tokyo, Japan). PPA-α and -β were identified in color photographs of the optic disc. Cross-sectional B-mode images of the peripapillary retina and sclera, including PPA-α and -β obtained with SD-OCT, were analyzed.

RESULTS. Of 120 normal eyes, 120 (100%) had PPA-α and 90 (75%) had PPA-β. In OCT images of the peripapillary retina, the ganglion cell layer and the inner and outer plexiform layers were observed to end in a tapering fashion at the edge of the optic disc, whereas the retinal nerve fiber layer continued into the optic cup. The external limiting membrane (ELM), inner–outer segments (IS-OS), and retinal pigment epithelium (RPE)/Bruch’s membrane complex were significantly more commonly absent before the optic disc edge within the PPA-β compared with areas outside the PPA-β (P < 0.0001). Specific findings in the peripapillary area including slope and step configurations of the scleral bed and hump- and wedge-shaped appearances of the RPE–Bruch’s membrane complex were identified in 63 (52.5%), 6 (5.0%), 19 (15.8%), and 6 (5.0%) of 120 eyes, respectively. The presence of the step configuration was associated with myopic and longer axial length (P = 0.0014 and 0.0105, respectively).

CONCLUSIONS. The cross-sectional anatomic configurations of the peripapillary atrophy were evaluated using SD-OCT. The termination of the retinal layers and configurations of the scleral bed in the peripapillary area varied among normal subjects. (Invest Ophthalmol Vis Sci. 2010;51:666–671) DOI: 10.1167/iovs.09-3663

P: Peripapillary atrophy (PPA), divided into zones β (PPA-β) and α (PPA-α), has been known to be associated with myopia and glaucoma, especially open-angle glaucoma with normal intraocular pressure.1–7 Studies of enucleated eyes have shown that PPA-β represents histologically a complete loss of retinal pigment epithelial (RPE) cells and an incomplete loss of adjacent photoreceptors, and PPA-α correlate with irregularities in the RPE.8–10 Both PPA-β and -α have been found to be significantly larger in eyes with glaucoma than in normal eyes, whereas the size, shape, and frequency of both PPA zones are not significantly different between normal eyes and eyes with optic neuropathy other than glaucoma.3–7,11,12

Optical coherence tomography (OCT) is a noninvasive, cross-sectional, optical topographic imaging technique. Its usefulness in imaging biological systems was first demonstrated with imaging of the peripapillary area of the retina.13 Recent advances in OCT, from conventional time domain (TD)-OCT to the new spectral domain (SD)-OCT, have resulted in improved imaging speeds and data-acquisition time, space resolution, and differentiation of retinal layers, as well as three-dimensional (3-D) reconstruction of the retina and optic nerve head images acquired although signal strength of SD-OCT follows a nonlinear function of the target depth from the focal plane.14–16 SD-OCT has been used to study in vivo macular and peripapillary nerve fiber layer thickness and diseases.17–25

The cross-sectional configurations of PPA has been studied in histologic investigations.8–10 Fantes and Anderson8 described peripapillary anatomic arrangements according to the alignment of the sclera, choroids, and RPE layers. Other histologic studies on PPA have shown the relationship of the RPE and photoreceptors at the peripapillary area as well as Bruch’s membrane changes with PPA.9,10 However, the number of eyes in the histologic studies on PPA are limited and those in which a noninvasive technique was used are not available. The purpose of the present study was to describe the cross-sectional configurations of the peripapillary retina and sclera, including PPA-α and -β in a large number of normal healthy eyes using the cross-sectional images obtained from SD-OCT and to correlate then with previous histologic reports.

METHODS

Ophthalmically normal subjects were recruited from two hospitals in Japan (University of Tokyo Hospital and Tajimi Municipal Hospital). Written informed consent was obtained from all subjects, and the study protocol had the approval of the hospitals’ ethics committee and was performed according to the tenets of the Declaration of Helsinki.

Subjects underwent complete ophthalmic examinations, including slit lamp biomicroscopy, gonioscopy, intraocular pressure (IOP), funduscopy, and axial length measurement (IOL Master; Carl Zeiss Meditec, Dublin, CA), as well as measurements of SD-OCT and visual field testing (Humphrey Field Analyzer 24-2 SITA Standard Program, [HFA];...
Carl Zeiss Meditec). Normal subjects were defined as: both eyes with best corrected visual acuity ≥20/25; intraocular pressure (IOP) of <21 mm Hg; refraction (SE, spherical equivalent) of ≤ –6.0 D; no findings suggesting the presence of ocular diseases, including glaucoma; no significant media opacities, including senile cataract that could affect SD-OCT and visual field testing; no history of intraocular surgeries; and no abnormal findings in a reliable (fixation loss <33% and false positive or negative <33%) visual field test. Abnormality of visual fields was determined according to the criteria of Anderson and Patella.24 The normal participants could have no other apparent ocular, neurosurgical, otolaryngological, or systemic disease that can cause optic nerve damage.

SD-OCT (3D OCT-1000; Topcon Corp., Tokyo, Japan) was used to obtain tomographic images of the parapapillary fundus. A superluminescent diode with center wavelength of 840 nm and bandwidth of 50 nm was used as the light source, resulting in an axial resolution of 6.1 μm in air and tissue, respectively. The spectrum of the interferometer output was detected with a spectrometer, which consisted of a collimating lens, transmission grating, imaging lens, and 2048-pixel line scan CCD camera, which was clocked at 40-MHz pixels, yielding a data acquisition rate of 18,700 axial scans, or 36 B-scans (512 axial scans/transverse pixels in each B-scan image, corresponding to 11.7 μm of distance between each axial scan) per second. 3-D data sets centered on the optic disc were obtained with a raster scan protocol of 512 × 128 axial scans (horizontal × vertical), which covered a 6 × 6-mm area with horizontal pixel spacing of 11 μm (6 mm/512) and vertical spacing of 47 μm (6 mm/128). The projection (en face) image of the OCT was first automatically transformed and aligned with a color fundus photograph (the reference structure) according to the information of the retinal vessel location. The projection image was further superimposed on the color fundus photograph and manually adjusted by an experienced examiner (Fig. 1). A color image of the optic disc and fundus with a view angle of 45° was acquired, with the fundus camera function (equivalent to that of a commercially available non-mydriatic fundus camera that is included in the same apparatus: TRC-NW200; Topcon Corp.), through the undilated pupil at the same time in the scanning protocol. The color optic disc photograph was used in the analysis of the presence or absence of PPA. In color fundus photographs, PPA-α was observed as having a complete loss of RPE cells, and PPA-α showed irregularities in the RPE.4-10 One eye of each subject was randomly selected for analysis. First, on a color fundus photograph, the presence of PPA-α and β was determined. The OCT images and optic disc photographs were analyzed by a single investigator (KYCL; Topcon 3D OCT-1000 Truemap Software, version 2.1; Topcon Corp.). The projection image of the OCT was aligned with the color photograph of the optic disc by manual overlay before analysis of the OCT images (Fig. 1). The cross-sectional configuration of the peripapillary area was evaluated on B-scan OCT images, in which vertical length was magnified four times compared with horizontal length. Because only horizontal raster scans were obtained, cross-sectional configuration of PPA could not be determined in the superior and inferior axes of the optic disc. Therefore, all B-scan OCT images between the 8- and 10-o’clock positions in the right eyes (or between the 2- and 4-o’clock positions in the left eyes) were evaluated. A mean of 17.6 ± 2.3 (range, 12–22) B-scans were analyzed for each eye. Because the B-scan images were horizontally

**Figure 1.** The overlay function. (A) The OCT scan image of the optic disc was manually overlapped with the colored optic disc photography to bring about an alignment of the images before B-scan analysis was performed (B).
obtained, only one or two scans analyzed pass through the optic disc center (at 3 or 9 o’clock). A specific configuration was considered positive when it was present in at least two consecutive B-scan images. Statistical analysis was performed including the Mann-Whitney U test for comparing means and Fisher’s exact test for comparing rates or prevalence. P < 0.05 was considered to be significant (SPSS 15.0J for Windows; SPSS Japan, Tokyo, Japan).

RESULTS

One hundred twenty eyes (63 right and 57 left eyes) of 120 normal subjects (61 men and 59 women) that fulfilled the criteria were analyzed. The mean ± SD age of the subjects was 53 ± 16 years (range, 21–77). The mean spherical equivalent (SE) refraction was −0.46 ± 1.80 D (range, −5.13–2.88), mean IOP was 13.9 ± 2.2 mm Hg (range, 10–18), and mean axial length was 23.8 ± 0.99 mm (range, 21.8–27.0). Of the 120 eyes, all (100%) had PPA-α and 90 (75.0%) had PPA-β with a significant difference in the prevalence (P < 0.0001, Fisher’s exact test).

On a B-scan image of the 3D-OCT, the optic cup, sclera, choroid, retinal pigment epithelium (RPE), and the retinal layers including the retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), and outer nuclear layers (ONL) were identifiable (Figs. 2A). The Bruch’s membrane could not be clearly distinguished from the RPE, and they are described herein as the RPE-Bruch’s membrane complex.

In the peripapillary area, the retinal layers, including GCL, IPL, INL, OPL, and ONL were observed to end in a tapering configuration before or at the edge of the optic disc, whereas the RNFL continued into the optic disc. The inner segment–outer segment junction of the photoreceptors (IS–OS) and external limiting membrane (ELM) could be traced to the edge of the optic disc or to the distal edge of the PPA-β in all 120 eyes.

A specific finding in the peripapillary retina corresponding to PPA-α was the gradual thinning of IS–OS and ELM on the PPA-α area as well as the gentle slope of the retinal tissues (Fig. 2B). The gradual thinning of the IS–OS and ELM was found in 104 (86.7%) of 120 eyes, but not in the remaining 16 eyes. No specific changes in thickness and reflection of the RPE-Bruch’s membrane complex were found in the PPA-α area on the OCT images.

In the retina corresponding to the area of PPA-β, irregularly higher intensities of the scleral layer, representing an absent (or depigmented) RPE layer, were found in all (100%) 90 eyes with PPA-β (Fig. 2C), suggesting that this finding in an OCT image is specific to the presence of PPA-β. In the area of PPA-β, the RNFL continued traveling into the optic disc. Most of the eyes without PPA-β, as well as the PPA-β-negative (−) locations in eyes with PPA-β, had the GCL, IPL, OPL, ELM, IS–OS, and RPE-Bruch’s membrane complex completely reaching the edge of the optic disc (Figs. 2A, 2B; Table 1). However, the disappearance of these layers before the optic disc edge was more frequently found in the PPA-β-positive (+) locations than in the PPA-β(−) locations in eyes with PPA-β or eyes without PPA-β (Figs. 3B, 3D, 3F; Table 1).

The scleral bed around the optic disc commonly formed a flat surface (Fig. 3B). However, the sloping edge of the scleral bed (Fig. 3D) was found in 62 (68.9%) of 90 eyes with PPA-β and 1 (3.3%) of 30 eyes without PPA-β (P < 0.0001, Fisher’s exact test, Table 2). There were no significant differences in sex, age, refractive error, axial length, and IOP between eyes with a sloping edge and those without (P > 0.10, Mann-Whitney test). Step configuration of the peripapillary scleral bed, in which a flat area was followed by a steep slope and then another flat area (Fig. 3F), was found in 6 (6.7%) of 90 eyes with PPA-β and in 0 (0%) of 30 without PPA-β (P = 0.3548). Step configuration was found only in PPA-β located in the inferotemporal half of the optic disc. Eyes with step configuration had more myopic refraction (−3.3 ± 1.7 D vs. −0.3 ± 1.7 D, P = 0.0014) and longer axial length than those without it (24.94 ± 1.26 mm vs. 23.69 ± 0.99 mm, P = 0.0105). Hump- and wedge-shaped appearances of the RPE-Bruch’s membrane complex were also found in the edge of the optic disc. A hump-shaped appearance resembling a road hump continued from the RPE layer in the OCT image, corresponding to the narrow crescent of hyperpigmentation on the color fundus photographs (Figs. 3G, 3H), and was found in 8 (8.9%) of 90 eyes with PPA-β and in 11 (36.7%) of 30 eyes without PPA-β (P = 0.0009). The wedge-shaped appearance was seen as an upward extension of the RPE-Bruch’s membrane complex at the edge of the optic disc (Fig. 3J), which was observed in 5 (5.6%) of 90 eyes with PPA-β.

### Table 1. Prevalence of Termination of the Retinal Layers before the Optic Disc Edge in Eyes with or without PPA-β

<table>
<thead>
<tr>
<th>Location</th>
<th>PPA-β(+)</th>
<th>PPA-β(−)</th>
<th>Total</th>
<th>Eyes without PPA-β</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCL</td>
<td>24/90 (26.7)</td>
<td>0/4 (0.0)</td>
<td>24/90 (26.7)</td>
<td>1/30 (3.3)</td>
<td>0.0044</td>
</tr>
<tr>
<td>IPL</td>
<td>26/90 (28.9)</td>
<td>0/4 (0.0)</td>
<td>26/90 (28.9)</td>
<td>1/30 (3.3)</td>
<td>0.0023</td>
</tr>
<tr>
<td>OPL</td>
<td>31/90 (34.4)</td>
<td>1/4 (25.0)</td>
<td>31/90 (34.4)</td>
<td>1/30 (3.3)</td>
<td>0.0006</td>
</tr>
<tr>
<td>ELM</td>
<td>31/90 (34.4)</td>
<td>1/4 (25.0)</td>
<td>31/90 (34.4)</td>
<td>1/30 (3.3)</td>
<td>0.0006</td>
</tr>
<tr>
<td>IS–OS junction of photoreceptors</td>
<td>90/90 (100)</td>
<td>2/4 (50.0)</td>
<td>90/90 (100)</td>
<td>10/30 (33.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RPE/Bruch’s membrane complex</td>
<td>90/90 (100)</td>
<td>1/4 (25.0)</td>
<td>90/90 (100)</td>
<td>1/30 (3.3)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are expressed as the number of eyes/total eyes in group (% of group). PPA-β(+), PPA-β-positive areas in eyes with PPA-β; PPA-β(−), PPA-β-negative areas in eyes with PPA-β.

PPA-β was defined as a complete loss of retinal pigment epithelial cells and PPA-α as irregularities in the RPE in color fundus photographs.

* Comparison of the prevalence between eyes with PPA-β (total) and those without (Fisher’s exact test).

† Comparison of the prevalence between locations with PPA-β and those without in eyes with PPA-β (Fisher’s exact test).
eyes with PPA-β and 1 (3.3%) of 30 eyes without PPA-β (P = 1.00). No significant difference was found between eyes with and without either wedge- or hump-shaped appearance for sex, age, refractive error, axial length, and IOP (P > 0.3).

**DISCUSSION**

The cross-sectional configurations of peripapillary retina including PPA-α and -β were imaged in vivo with SD-OCT in 120 normal subjects in the present study. With regard to anatomic arrangement of the peripapillary retina, only histologic studies based on enucleated eyes have been available, but the number of eyes studied was limited.4-8,10 Because of the small number of eyes, the prevalence of the histologic findings was difficult to determine, and it was impossible to assess the association of the findings with demographic factors such as age and refractive error.

The layers of the retina—RNFL, GCL, OPL, IPL, ELM, IS–OS, and RPE–Bruch’s membrane—were visible from the OCT images, and we described how these layers appear in the peripapillary region in vivo. Of note was the tapering configuration of the RNFL, GCL, OPL, and IPL layers as the edge of the optic disc was approached. The RNFL continued into the optic disc while the GCL, OPL, and IPL layers were imaged in vivo with SD-OCT in 120 normal subjects in the present study. With regard to anatomic arrangement of the peripapillary retina, only histologic studies based on enucleated eyes have been available, but the number of eyes studied was limited.4-8,10 Because of the small number of eyes, the prevalence of the histologic findings was difficult to determine, and it was impossible to assess the association of the findings with demographic factors such as age and refractive error.

In the present study, all eyes had PPA-α, which was not far from previous results on the prevalence of PPA in normal populations.4,5 The findings in the cross-sectional images of OCT corresponding to the PPA-α area were similar to those in the peripapillary areas without PPA-α, except for a tapering decline and loss of density of the IS–OS layer toward the optic disc edge. This decline could represent the gradual loss of photoreceptors at the PPA area as the RNFL changes correlating to PPA-α develop.10 On the other hand, irregularities of RPE, which was a histologic definition of PPA-α,3,7 were not detected in the current OCT images. The spatial resolution of the SD-OCT (≈6 μm in z-axis) may not be enough to depict the scanty changes in the RPE in PPA-α although the resolution has been improved from that of a TD-OCT.

According to previous histologic evidence, there is no RPE (or if present, it is depigmented) in the PPA-β zone,8,9 and this was supported from our OCT images of the PPA-β, which showed light transmission to the deeper layers in the PPA-β zone in the OCT images. Because this higher intensity of the scleral layer was found in all eyes with PPA-β, PPA-β can be determined by this specific finding on an OCT image without the aid of color fundus photographs. The arrangement of the GCL, IPL, and OPL layers in PPA-β region were similar to the peripapillary areas without PPA-β in that the layers terminate in a tapering fashion. We observed significantly, however, that with the presence of PPA-β, these layers terminate earlier than the optic disc edge and a small percentage of these layers terminate before the distal edge of PPA-β. This could be the result of the loss of the photoreceptors and hence the resultant degeneration of the layers above them, altering the configuration of PPA in the PPA-β region.

In the present study, the scleral bed around the optic disc was usually found to be flat, whereas other specific appearances of the scleral bed or RPE–Bruch’s membrane complex were identified. The sloping edge of the scleral bed was frequently encountered in eyes with PPA-β as well as in the area...
of PPA-β. We cannot rule out that this sloping edge configuration was an acquired change from an initial flat configuration with the progressive loss of the retinal layers as PPA developed. Prospective studies determining whether the PPA flat configuration changes to a sloping edge configuration over time are needed. Step configuration of the peripapillary scleral bed, which was found only in the PPA-β area, was significantly associated with myopia and eyes with longer axial length. This configuration could represent an underlying scleral susceptibility to stretching or deformation in myopic eyes, as well as the anatomic direction of the optic nerve as it enters the sclera. In our cohort of eyes, this configuration occurred exclusively in PPA-β located in the inferotemporal half of the optic disc, and it would be interesting to determine the frequency and relationship of this configuration in patients who are myopic and have glaucoma, because correlation between PPA area and visual field damage in glaucomatous eyes is reportedly stronger in the inferior part of the optic disc than in the superior part.25

Hump- and wedge-shaped appearances of the RPE-Bruch’s membrane are most likely developmental in origin, as they correlate with the developmental changes noted in previous histologic studies.8,10 The eye cup invaginates during embryonic development and forms the neuroectoderm, which is double layered: the outer layer forming the RPE and the inner layer of the retina. The two layers are continued at the disc margin as a fold in the neuroectoderm. This fold may be the wedge-shaped appearance found in our study, with the wedge representing the folded RPE-Bruch’s membrane. Fantes and Anderson8 described a double-layered RPE seen on histology and clinically as a narrow crescent of intense pigmentation. This pigmentation resulted from the fold within the PPA area and is thought to be represented by the hump-shaped appearance in our study.

In the present study, because only horizontal raster scans were obtained, only B-scan OCT images between the 8- and 10-o’clock positions in the right eyes (or between the 2- and 4-o’clock positions in the left eyes) were evaluated. In the strict sense, only one or two scans passed through the optic disc center and the images in the other scans may be a bit oblique to the meridian of the optic disc. Since the present study was a qualitative analysis that mainly focused on the presence of the retinal layers and the scleral configurations in the peripapillary area, the influence of the modestly oblique cut of the optic disc should be minor. However, when quantitative analysis is attempted in future studies, the influence of the oblique cut should be carefully excluded or adjusted, or the usage of radial scans of the optic disc should be considered.

In conclusion, SD-OCT imaging of the PPA area in most of the eyes showed that the RNFL, GCL, IPL, and OPL tapered toward the edge of the optic disc with the RNFL continuing into the optic cup, whereas the IS-OS junction of photoreceptors, together with the ELM, ended abruptly at the distal edge of the PPA-β. Specific appearances in the PPA area were identified in our cohort of normal eyes by SD-OCT. The step configuration of the scleral bed was associated with myopia and longer axial lengths, whereas the sloping edge of scleral bed and the hump- and wedge-shaped appearance of the RPE-Bruch’s membrane complex were not significantly associated with sex, age, refractive error, axial length, or IOP. The current results deserve further investigation regarding the association of these findings with pathologic conditions of the optic disc and peripapillary retina, such as glaucoma and pathologic high myopia.

References


