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Ten Years and Beyond Longitudinal Change of ß-Zone Parapapillary Atrophy

Comparison of Primary Open-Angle Glaucoma with Normal Eyes

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Purpose: To investigate the difference in longitudinal change of ß-zone parapapillary atrophy (PPA) between eyes with primary open-angle glaucoma (POAG) and normal eyes.

Design: Longitudinal, observation study.

Participants: A total of 153 eyes with POAG and 105 normal eyes.

Methods: Participants were followed for 10 years or more, with disc photography performed every year. The topographic parameters of ß-zone PPA (area, maximal radial extent, angular extent around disc) were measured. The factors associated with the enlargement of ß-zone PPA parameters were assessed by odds ratio (OR) using multivariable logistic regression.

Main Outcome Measures: Enlargement of ß-zone PPA parameters and associated factors.

Results: Over the course of the average 11.6±1.3-year follow-up period, enlargement of β-zone PPA was detected in 66.7% of POAG eyes and in 26.7% of normal eyes. Increment of all PPA parameters was significantly more common in cases of POAG than in normal eyes (all $P < 0.001$). The spatial distribution of maximal radial extent at baseline and final examination was significantly different between the 2 groups: POAG eyes; infero-temporal versus normal eyes; temporal (chi-square = 26.549, $P < 0.001$, chi-square = 19.320, $P = 0.004$, respectively). The widening of radial extent was significantly associated with older age (OR, 1.036; $P = 0.010$) and the presence of glaucoma (OR, 2.599; $P = 0.002$). The increment of angular extent was associated with the presence of glaucoma (OR, 12.167; $P = 0.017$) and optic disc hemorrhage (OR, 3.266; $P = 0.019$).

Conclusions: The pattern of ß-zone PPA change differed between POAG and normal eyes during a follow-up of 10 years or more. The enlargement of PPA occurred more frequently in POAG than in normal eyes. The widening of radial extent was associated with older age and glaucoma, whereas the increment of angular extent was associated with glaucomatous damage. *Ophthalmology 2020;127:1054-1063 © 2020 by the American Academy of Ophthalmology*

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In glaucomatous optic neuropathy, a variety of morphologic changes of the optic nerve head are demonstrated, including optic cup deepening, neuroretinal rim loss, optic disc hemorrhage, localized or generalized retinal nerve fiber layer (RNFL) defect, and parapapillary atrophy (PPA).[1] ß-zone PPA is known to be associated with glaucoma and is characterized by marked atrophy of the retinal pigment epithelium (RPE) and choriocapillaris, with good visibility of the sclera and large choroidal vessels.[2,3]

The association between ß-zone PPA and glaucoma has been widely investigated. ß-zone PPA is notably more common and larger in eyes with glaucoma than in normal eyes.[2,4,5] The location significantly correlates with optic disc cupping,[2] neuroretinal rim loss,[5] optic disc hemorrhage,[6,7] angular location of RNFL defect,[8] and visual field (VF) damage.[2] Also, the region of ß-zone PPA significantly correlates with the degree of optic disc damage and VF defects.[5,9-11]

ß-zone PPA is seen not only in individuals with glaucoma but also in normal individuals. Previous studies have demonstrated that ß-zone PPA enlarges in some eyes as glaucoma progresses[12-17] but in some others with age.[13] Although longitudinal change of ß-zone PPA is well studied in glaucomatous eyes, to our knowledge, comparison of glaucomatous eyes with normal eyes is limited.[18] Moreover, the issues of whether ß-zone PPA progresses in normal eyes and the difference in its pattern compared with glaucomatous eyes are unclear.

In this longitudinal study covering 10 years and more of follow-up, we investigated the change of morphologic

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features in β-zone PPA between eyes with primary open-angle glaucoma (POAG) and normal controls. Additionally, factors associated with change of β-zone PPA topographic parameters were explored.

Methods

This study was approved by the Seoul National University Hospital Institutional Review Board, and informed consent was waived because of the study's retrospective nature. All of the specific investigations adhered to the tenets of the Declaration of Helsinki.

Study Subjects

All of the subjects were examined at the Seoul National University Hospital Glaucoma Clinic in Seoul, Korea, between June 2004 and June 2018. Eligible participants were enrolled, consecutively, on the basis of a retrospective medical records review.

The subjects included in the study had clearly detectable ß-zone PPA at baseline and had undergone disc photography every year for 10 or more years. Diagnosis of POAG was defined as follows: the presence of glaucomatous optic disc change (e.g., focal notching, thinning of rim, and RNFL defect); a glaucomatous VF defect corresponding to structural change; and an open angle. ß-zone PPA was considered not to be a criterion for classification of glaucomatous optic neuropathy. Glaucomatous VF defect was defined as (1) glaucoma hemifield test values outside the normal limits; (2) 3 or more abnormal contiguous points with a probability of $P < 0.05$, of which at least 1 point has a probability of $P < 0.01$ on a pattern deviation plot; or (3) a pattern standard deviation of $P < 0.05$. Visual field defects were confirmed on 2 consecutive reliable tests (fixation loss rate $\leq$20%, false-positive and false-negative error rates $\leq$25%). All of the subjects were treated with 1 or more topical glaucoma medication.

For the control group, subjects who had been regularly examined for cataract or a family history of glaucoma were included consecutively. The following criteria had to be met: (1) baseline intraocular pressure (IOP) less than 21 mmHg, with no history of elevated IOP; (2) normal optic disc and retina; and (3) normal VF test result.

Subjects were excluded from further analysis for any of the following reasons: best-corrected visual acuity <20/40 (in Snellen equivalent); spherical equivalence <−6.0 diopters (D) or >+3.0 D; history of intraocular surgery (except uncomplicated cataract extraction); history of uveitis or inflammatory disease; and any retinal or neurologic disease possibly affecting the VF examination results. We required good-quality disc photographs and OCT images; poor-quality photographs that would render ß-zone PPA border identification difficult were excluded. If both eyes were eligible according to the inclusion criteria, 1 eye was selected randomly for further study.

All of the enrolled patients had undergone a complete ophthalmic examination, including visual acuity assessment, refraction, slit-lamp biomicroscopy, Goldmann applanation tonometry (Haag-Streit, Koniz, Switzerland), central corneal thickness measurement (Orbscan 73 II, Bausch & Lomb Surgical, Rochester, NY), axial length measurement (Axis II PR; Quantel Medical, Inc., Bozeman, MT), dilated fundus examination, digital color disc photography, red-free RNFL photography (TRC-50IX; Topcon Corporation, Tokyo, Japan), optic nerve head imaging by Cirrus spectral domain OCT (Carl Zeiss Meditec, Dublin, CA), and standard automated perimetry 30-2 testing (Humphrey Field Analyzer; Carl Zeiss Meditec).

Evaluation of Optic Disc Images and ß-Zone Parapapillary Atrophy

All of the disc photographs had been obtained after dilation of the pupil and were taken with a simultaneous fundus camera, scanned, and saved. Images were saved in a 1600×1216-pixel digital imaging format and stored in the picture-archiving communication system of Seoul National University Hospital. Serial disc photographs were evaluated thoroughly during the total follow-up period. ß-zone PPA was defined on the basis of a disc photograph evaluation as follows: an area adjacent to the disc margin with notable atrophy of the RPE, visible sclera, and visibly large choroidal vessels. This is as opposed to α-zone PPA, which manifests as an outer irregular area with hyperpigmentation and hypopigmentation. Also, with the use of OCT, OCT-defined β-zone (PPA with Bruch's membrane) and gamma (γ)-zone (PPA without Bruch's membrane) were evaluated as previously described.[19] One glaucoma specialist (Y.K.K.) masked to the patients' clinical information reviewed by double-checking all of the OCT results showing sufficient image quality.

Planimetric Measurement of ß-Zone Parapapillary Atrophy

The topographic parameters of ß-zone PPA were (1) area, (2) maximal radial extent (width), and (3) angular extent around the disc (circumference), as described in Figure 1. The pixel areas of β-zone PPA and clinical disc were obtained by ImageJ software (V.1.48; developed by Wayne Rasband, National Institute of Health, Bethesda, MD). The area was plotted using a mouse-driven cursor to trace the PPA and disc margins directly onto the disc photograph image. The structures for quantification were outlined on the inside edge in order that the trace thickness could be incorporated into the total delineated area. The pixel areas (in square millimeters) were calculated by a formula for optic disc area correction using disc photography and spectral-domain OCT; this procedure has been described in detail by others.[20,21] By using the disc-to-PPA ratio, the real area and maximal radial extent of ß-zone PPA were calculated. The spatial distribution of maximal radial extent was recorded in terms of clock hours around the disc; the right eye was measured clockwise, and the left eye was measured counterclockwise. They were divided into sectors, corresponding to 1 VF region based on the retinotopic projection of the VF onto the disc:[22,23] inferotemporal sector (7 to 8 o'clock), horizontal temporal sector (9 o'clock), superotemporal sector (10 to 11 o'clock), superior sector (12 o'clock), superonasal sector (1 to 3 o'clock), inferonasal sector (3 to 5 o'clock), and inferior sector (6 o'clock). The circumferential angular extent was measured in degrees from the angle made at the center of the disc.[12]

All of the PPA parameters were measured independently by 2 glaucoma specialists (E.B. and A.H.). Images were evaluated in a masked fashion without knowledge of the patients' clinical diagnosis or any other clinical information. The measurements were performed 3 times for each patient at intervals of at least 1 day, and the representative value was considered to be the average of 3 measurements.

Assessment of Parapapillary Atrophy Enlargement

All ß-zone PPA parameter measurements for each subject at baseline and final visit were compared. We used the Bland−Altman method to establish a criterion for PPA enlargement.[24,25] This tool has been used for identification of changes in

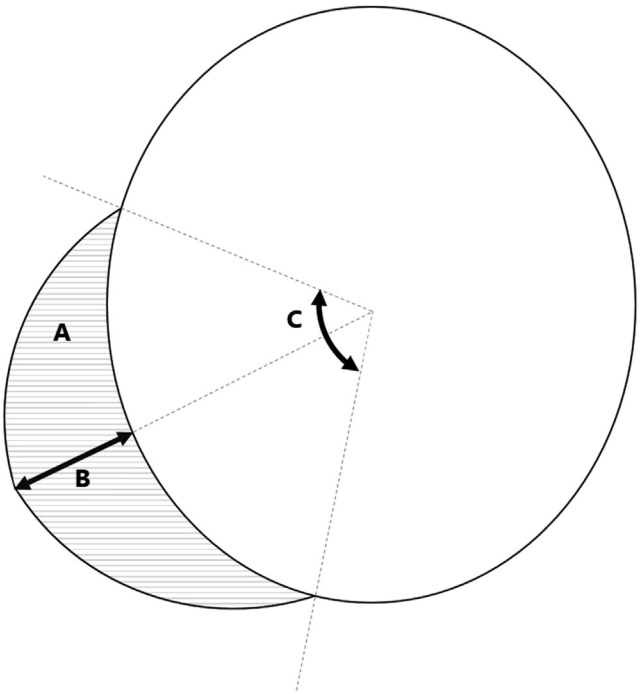

Figure 1. The parameters of ß-zone parapapillary atrophy (PPA) were (**A**) area, (**B**) maximal radial extent, and (**C**) angular extent. The location of maximal radial extent was recorded in terms of clock hours around the disc. The angular extent around the optic disc was measured in degrees from the angle made at the center of the disc.

repeated visual acuity measurements.[26-29] The cutoff for determination of enlargement was the limit of agreement for test−retest variability. ß-zone PPA enlargement was deemed statistically significant in cases where it exceeded 1.96 times the intersession standard deviation, because this corresponds to the 95% confidence interval (CI) for the true value of the measurement.[30-33] The intersession standard deviation of ß-zone PPA was calculated as the test−retest variability between paired measurements repeated at 30-minute intervals in 10 healthy normal subjects not enrolled in the study. The ß-zone PPA enlargement parameters were defined as discussed next.

Final Measurement Greater than Initial Measurement × 1.96 Times the Intersession Standard Deviation

The ß-zone PPA enlargement parameters were determined in terms of (1) enlargement of area, (2) enlargement of radial extent, and (3) enlargement of angular extent. In patients with enlargement of radial extent, the change of spatial distribution of maximum radial extent was evaluated. This was considered in terms of the clock-hour location of the maximum radial extent at the final visit.

Data Analysis

The subjects' characteristics were compared by independent Student *t* test for normally distributed data and analyzed by chi-square testing for categoric data. Intergroup ß-zone PPA parameter differences were assessed using the chi-square test. The change of the final from the initial ß-zone PPA measurement was compared between the groups by 1-way analysis of variance. The Bonferroni correction was applied to adjust the impact of multiple comparisons. To determine the interobserver measurement reproducibility of the ß-zone PPA measurements, the intraclass correlation coefficient with its CI was calculated by 2 independent examiners (E.B. and A.H.). The odds ratio (OR) of ß-zone PPA enlargement was estimated with covariates. The following variables were initially analyzed in a univariate model: age, gender, hypertension, diabetes mellitus, follow-up period, refractive error spherical equivalence, axial length, central corneal thickness, baseline IOP, optic disc hemorrhage, diagnosis of glaucoma, and optic nerve head parameters. The variables that retained significance at $P < 0.10$ were included in a subsequent multivariate model. Before multiple linear regression analysis, multicollinearity among the variables was confirmed. The final multivariate model was developed by means of backward elimination, and ORs with 95% CIs were calculated. Statistical analyses were performed with the Statistical Package for Social Sciences version 21.0 for Windows (SPSS, Inc., Chicago, IL). A P value < 0.05 was considered to represent statistical significance.

Results

Initially, 296 eyes meeting the eligibility criteria were enrolled. Among them, 38 were excluded because the disc photographs had poor image quality. Eventually, 258 eyes (153 POAG and 105 normal eyes) met the final entry criteria.

Demographic and Clinical Characteristics of Study Subjects

In all of the included study eyes, the mean follow-up period was 11.6±1.3 years, and the mean number of disc photographs was 13.8±1.7. The mean age at baseline was 56.8±11.2 years (range, 26−80 years); among the subjects, 122 were men (47.3%), and 136 were women (52.7%). A summary comparison of the baseline characteristics between the POAG and normal subjects is provided in Table 1. Patients with POAG had higher baseline IOP (15.5±2.8 vs. 13.8±2.7 mmHg, $P < 0.001$) than did normal subjects, more frequent optic disc hemorrhage (21.6 vs. 8.6%, $P = 0.008$), larger average and vertical cup-to-disc ratio (0.73±0.11 vs. 0.66±0.11, 0.72±0.10 vs. 0.61±0.12, all $P < 0.001$, respectively), smaller rim area (0.90±0.22 vs. 1.12±0.21 mm^2, $P < 0.001$), and a worse mean deviation (MD) value (−1.27±1.68 vs. −0.54±1.75, $P = 0.001$).

Reproducibility of Measurements

The interobserver intraclass correlation coefficients for ß-zone PPA area, maximal radial extent, and angular extent were 0.89, 0.82, and 0.86 (95% CIs, 0.83−0.95, 0.79−0.88, and 0.82−0.90, respectively). These values indicated excellent agreement for all of the measurements.[34]

Baseline Measurement of β-Zone Parapapillary Atrophy

The mean area and angular extent of PPA were significantly larger in POAG eyes than in normal eyes: 0.89±0.52 mm^2 vs. 0.73±0.41 mm^2 and 245.8°±91.4° vs. 224.9°±92.7° ($P = 0.019$ and $P = 0.049$, respectively). The radial extent did not show any significant difference between the POAG and normal eyes: 0.40±0.17 mm vs. 0.38±0.15 mm ($P = 0.56$) (Table 1). With reliable OCT images of 102 eyes in the glaucoma group and 82 eyes in the normal group, all of the eyes in both groups presented OCT-defined β-zone without significant difference ($P > 0.99$). The γ-zone PPA was detected in 35 eyes in the glaucoma group and 27 eyes in the normal group, without statistical significance ($P = 0.84$).

Table 1. Comparison of Demographic and Clinical Characteristics Between Open-angle Glaucoma and Normal Subjects with ß-Zone Parapapillary Atrophy

	Normal (n = 105)	Glaucoma (n = 153)	*P* Value
Demographic Data			
Age (yrs)	67.9±12.2	68.6±10.3	0.91*
Male, n (%)	42 (40.0)	80 (52.3)	0.06†
Hypertension, n (%)	43 (40.9)	64 (41.8)	0.96†
Diabetes mellitus, n (%)	13 (12.4)	21 (13.7)	0.78†
Follow-up duration (yrs)	11.5±1.7	11.7±1.8	0.51*
Clinical Data			
Spherical equivalence (D)	−0.57±2.12	−1.06±2.56	0.61*
Axial length (mm)	23.80±0.93	24.57±2.78	0.11*
Central corneal thickness (μm)	546.5±32.2	539.3±42.1	0.37*
Baseline IOP	13.8±2.7	15.5±2.8	<0.001*
Optic disc hemorrhage, n (%)	9 (8.6)	33 (21.6)	0.008†
Optic Nerve Head Parameter			
Average CDR	0.66±0.11	0.73±0.11	<0.001*
Vertical CDR	0.61±0.12	0.72±0.10	<0.001*
Disc area (mm^2)	2.11±0.43	2.16±0.45	0.19*
Rim area (mm^2)	1.12±0.21	0.90±0.22	<0.001*
Functional Parameter			
MD (dB)	−0.54±1.75	−1.27±1.68	0.001*
ß-Zone PPA Parameter			
Area (mm^2)	0.73±0.41	0.89±0.52	0.019*
Radial extent (mm)	0.38±0.15	0.40±0.17	0.56*
Angular extent (°)	224.9±92.7	245.8±91.4	0.049*

CDR = cup-to-disc ratio; D = diopters; dB = decibels; IOP = intraocular pressure; MD = mean deviation; PPA = parapapillary atrophy.
*Student *t* test.
†Chi-square test.

Enlargement of β-Zone Parapapillary Atrophy

During the follow-up, the POAG group showed significant enlargement in all of the ß-zone PPA parameters relative to the normal group (area: 66.7% vs. 26.7%, radial extent: 62.1% vs. 20.0%, angular extent: 20.3% vs. 2.7%, all *P* values < 0.001, Table 2). Table S1 (available at www.aaojournal.org) shows the values of the ß-zone PPA parameters at the baseline and final visit. The area of ß-zone PPA significantly increased in the normal eyes, and all of the parameters of ß-zone PPA showed significant enlargement in POAG eyes.

Table 3 compares the spatial distribution of maximal radial extent of ß-zone PPA between the normal and POAG eyes. The majority of radial extent was located in the inferotemporal, temporal, and superotemporal areas. The most common location at initial and final was the inferotemporal in POAG eyes and the temporal in normal eyes. The baseline location and pattern of ß-zone PPA change showed significant differences between the 2 groups (chi-square = 26.549, $P < 0.001$, chi-square = 19.320, $P = 0.004$, respectively).

Factors Associated with Enlargement of β-Zone Parapapillary Atrophy

The baseline factors associated with enlargement of β-zone PPA were analyzed by univariate and multivariable analyses for all of the included eyes. The factors (2 factors) associated with enlargement of area were older age (OR, 1.054, 95% CI, 1.016−1.094, $P = 0.005$) and the presence of glaucoma (OR, 10.907, 95% CI, 4.351−25.344, $P < 0.001$) (Table 4). The factors (2 factors) associated with enlargement of radial extent were older age (OR, 1.036, 95% CI, 1.008−1.064, $P = 0.010$) and the presence of glaucoma (OR, 2.599, 95% CI, 1.404−4.810, $P = 0.002$) (Table 5). The 2 factors associated with the enlargement of angular extent were the presence of glaucoma (OR, 12.167, 95% CI, 1.532−45.644, $P = 0.017$) and optic disc hemorrhage (OR, 3.266, 95% CI, 1.220−8.747, $P = 0.019$) (Table 6).

Table 2. Comparison of ß-Zone Parapapillary Atrophy Enlargement Between Open-angle Glaucoma and Normal Subjects

	Normal (n = 105)	Glaucoma (n = 153)	*P* Value*
Area (mm^2)	28 (26.7)	102 (66.7)	**<0.001**
Radial extent (mm)	21 (20.0)	95 (62.1)	**<0.001**
Angular extent (°)	3 (2.7)	31 (20.3)	**<0.001**

Comparison was performed using chi-square test.
*Bonferroni correction for multiple comparisons. Values with statistical significance are shown in boldface.

Age Distribution Associated with β-Zone Parapapillary Atrophy Enlargement

The subjects were divided into 4 subgroups according to age at first visit: <50 years, 50−59 years, 60−69 years, and 70−79 years. The frequency distribution of β-zone PPA enlargement compared between the POAG and normal subjects is plotted in Figure 2. The proportion of eyes showing β-zone PPA enlargement increased with age, with statistical significance in POAG eyes ($P = 0.012$) and marginal significance in normal eyes ($P = 0.20$).

Representative Cases

Figure 3 highlights representative cases comparing a normal eye without β-zone PPA enlargement and a POAG eye with β-zone PPA enlargement during 10 years of follow-up. Figure 4 presents disc photographs of subjects initially and after the 10-year follow-up period as grouped by initial age.

Discussion

In this longitudinal study with a follow-up period of 10 years or more, we determined and analyzed the change of β-zone PPA in POAG compared with normal eyes. Additionally, we evaluated factors associated with β-zone PPA enlargement.

The association of β-zone PPA and glaucoma has been widely studied using morphometric techniques. The presence of β-zone PPA, which increases the risk of glaucoma progression,[35] is useful for the purposes of early diagnosis of glaucoma.[36-38] Longitudinal investigations have documented that the development or enlargement of β-zone PPA is associated with progression of glaucoma.[11,18,35] In this study, we found that POAG eyes were significantly associated with enlargement of all of the topographic parameters of β-zone PPA. Because many variables were analyzed by multiple comparisons, Bonferroni adjustment was applied to ensure the validity of the data.[39]

Table 3. Baseline Spatial Distribution and Final Location of Enlargement of Maximum Radial Extent of ß-Zone Parapapillary Atrophy in Normal and Open-angle Glaucoma Subjects

	Baseline Location				Final Location of Enlargement			
	Total (n = 258)	*Normal (n = 105)*	*Glaucoma (n = 153)*	P *Value**	*Total (n = 120)*	*Normal (n = 23)*	*Glaucoma (n = 97)*	P *Value**
Inferotemporal	133 (51.6)	26 (24.8)	90 (58.8)	**<0.001**	69 (57.5)	4 (17.4)	58 (59.8)	**0.004**
Temporal	52 (20.2)	54 (51.4)	15 (9.8)		13 (10.8)	13 (56.0)	7 (7.2)	
Superotemporal	48 (18.6)	14 (13.3)	34 (22.2)		22 (18.3)	1 (4.3)	21 (21.6)	
Superior	1 (0.4)	1 (0.9)	0 (0.0)		2 (1.7)	2 (8.7)	0 (0.0)	
Superonasal	5 (1.9)	3 (2.8)	2 (1.3)		2 (1.7)	1 (4.3)	1 (1.0)	
Inferonasal	8 (3.1)	4 (3.8)	4 (2.6)		6 (5.0)	1 (4.3)	5 (4.2)	
Inferior	11 (4.3)	3 (2.8)	8 (5.2)		6 (5.0)	1 (4.3)	5 (4.2)	

Comparison was performed using chi-square test.
*Bonferroni correction for multiple comparisons. Values with statistical significance are shown in boldface.

β-zone PPA has been observed in 10% to 20% of normal eyes.[40-42] In a population-based study, the progression rate of β-zone PPA in nonhighly myopic, nonglaucomatous subjects was 6.6% and showed associations with variable factors, including older age.[18] Likewise, in the present study, the enlargement of area and radial extent were associated with older age. This may be explained by age-related degeneration,[13,43] including physiologic age-related loss in approximately 0.3% of retinal photoreceptors and RPE cells per year in life.[44] Moreover, the enlargement pattern in normal eyes was based mainly on radial increment. Therefore, we can assume that in normal eyes, enlargement of β-zone PPA occurs mainly by widening and that age-related change occurs radially outward from the optic nerve head. This is consistent with histopathology studies on β-zone PPA.[45,46] In normal eyes, the length of β-zone PPA is significantly wider among the oldest eyes, and an association between aging and unidirectional spread of RPE degeneration, radially outward from the optic nerve head, has been posited.[45]

The spatial distribution of maximal radial extent of β-zone PPA showed a significant difference between the POAG and normal eyes in the present study. In POAG, the most common location was the inferotemporal area, followed by the superotemporal. Contrastingly, in normal eyes, the most common location was the temporal area. The location of β-zone PPA radial extent in POAG corresponded to the most frequent site of RNFL defect in glaucoma.[47,48] This fact is consistent with a previous report demonstrating that the angular location of localized RNFL defect correlated spatially with β-zone PPA's maximal radial extent.[8]

The factors associated with the enlargement of radial and angular extent of β-zone PPA also showed differences. The increment of radial extent was associated with older age and glaucoma, whereas the increment of angular extent was

Table 4. Univariate and Multivariate Model of Factors Associated with Enlargement of Area of ß-Zone Parapapillary Atrophy

	Univariate Model				Multivariate Model			
Variable	*Beta*	*Wald*	*OR (95% CI)*	P *Value*	*Beta*	*Wald*	*OR (95% CI)*	P *Value*
Demographic Variable								
Age, yrs	0.030	6.680	1.031 (1.007–1.055)	0.010	**0.053**	**7.921**	**1.054 (1.016–1.094)**	**0.005**
Sex, male	0.000	0.000	1.000 (0.613–1.630)	0.99				
Hypertension	0.148	0.338	1.159 (0.705–1.907)	0.56				
Diabetes mellitus	−0.145	0.154	0.865 (0.420–1.783)	0.70				
Follow-up duration, yrs	−0.022	0.001	1.002 (0.870–1.153)	0.97				
Clinical variable								
Spherical equivalence, D	0.025	0.224	1.025 (0.925–1.135)	0.64				
Axial length, mm	0.009	0.008	1.009 (0.839–1.212)	0.93				
Central corneal thickness, μm	−0.008	0.005	0.992 (0.983–1.002)	0.09	−0.004	0.593	0.996 (0.987–1.007)	0.44
Baseline IOP, mmHg	0.040	0.820	1.040 (0.955–1.133)	0.37				
Optic disc hemorrhage	0.672	3.860	1.958 (1.002–3.827)	0.049	0.737	1.949	2.090 (0.742–5.884)	0.16
Diagnosis of glaucoma	1.754	38.812	5.778 (3.327–10.033)	<0.001	**2.389**	**25.967**	**10.907 (4.351–27.344)**	**<0.001**
Optic nerve head parameter								
Baseline average CDR	0.456	12.663	1.577 (1.227–2.028)	<0.001	0.366	2.002	1.441 (0.869–2.391)	0.16
Baseline vertical CDR	0.550	18.871	1.733 (1.352–2.221)	<0.001				
Baseline disc area, mm^2	0.670	5.102	1.954 (1.093–3.495)	0.024				
Baseline rim area, mm^2	−1.357	6.191	0.257 (0.088–0.750)	0.013	1.184	1.173	3.267 (0.383–27.832)	0.28

CDR = cup-to-disc ratio; CI = confidence interval; D = diopters; IOP = intraocular pressure; OR = odds ratio.
Values with statistical significance are shown in boldface.

Table 5. Univariate and Multivariate Model of Factors Associated with Enlargement of Radial Extent of ß-Zone Parapapillary Atrophy

Variable	Univariate Model				Multivariate Model			
	Beta	*Wald*	*OR (95% CI)*	P *Value*	*Beta*	*Wald*	*OR (95% CI)*	P *Value*
Demographic Variable								
Age, yrs	0.036	8.068	1.037 (1.011–1.063)	0.005	**0.035**	**6.655**	**1.036 (1.008–1.064)**	**0.010**
Sex, male	0.170	0.425	1.185 (0.711–1.977)	0.52				
Hypertension	0.236	0.804	1.266 (0.756–2.122)	0.37				
Diabetes mellitus	−0.880	3.891	0.415 (0.173–0.994)	0.40				
Follow-up period, yrs	−0.005	0.004	0.995 (0.860–1.153)	0.95				
Clinical variable								
Spherical equivalence, D	0.036	0.421	1.037 (0.930–1.155)	0.52				
Axial length, mm	0.024	0.067	1.024 (0.855–1.227)	0.80				
Central corneal thickness, µm	−0.006	1.768	0.994 (0.986–1.003)	0.18				
Baseline IOP, mmHg	0.033	0.532	1.033 (0.946–1.129)	0.47				
Optic disc hemorrhage	0.384	1.299	1.468 (0.759–2.840)	0.25				
Diagnosis of glaucoma	1.075	14.068	2.929 (1.670–5.135)	<0.001	**0.955**	**9.246**	**2.599 (1.404–4.810)**	**0.002**
Optic nerve head parameter								
Baseline average CDR	0.221	3.193	1.247 (0.979–1.589)	0.07	0.405	0.115	1.046 (0.808–1.353)	0.73
Baseline vertical CDR	0.267	5.001	1.306 (1.034–1.650)	0.025				
Baseline disc area, mm^2	0.448	2.271	1.566 (0.874–2.806)	0.13				
Baseline rim area, mm^2	−0.406	0.551	0.667 (0.229–1.944)	0.46				

CDR = cup-to-disc ratio; CI = confidence interval; D = diopters; IOP = intraocular pressure; OR = odds ratio.
Values with statistical significance are shown in boldface.

associated with glaucoma and optic disc hemorrhage, a frequently manifested change in glaucoma. Several studies have found that PPA and disc hemorrhage tend to occur in the same regions,[6,7,49,50] and other investigators have reported that the angular extent of PPA is greater in glaucomatous eyes with disc hemorrhage.[6,51] Accordingly, we can assume that enlargement of angular extent of β-zone PPA is an aspect of glaucomatous damage.

Enlargement of β-zone was confirmed in 66.7% of POAG eyes and 26.7% of normal eyes. These contrasting results with respect to the data presented in other reports (6.2%–65.0% in POAG and 0%–7.4% in normal eyes)[15,18,52] can be explained in several ways. First, the present study had a longer mean follow-up period (>10 years) than the relevant earlier studies (<5 years). Second, our study excluded highly myopic subjects, whereas 2 of the earlier studies included them.[18,52] Third, we defined progression of PPA differently, which is to say, by quantitative measurement using the Bland–Altman method, whereas earlier studies defined it qualitatively as

Table 6. Univariate and Multivariate Model of Factors Associated with Enlargement of Angular Extent of ß-Zone Parapapillary Atrophy

Variable	Univariate Model				Multivariate Model			
	Beta	*Wald*	*OR (95% CI)*	P *Value*	*Beta*	*Wald*	*OR (95% CI)*	P *Value*
Demographic Variable								
Age, yrs	0.006	0.129	1.006 (0.974–1.038)	0.72				
Sex, male	−0.064	0.032	0.938 (0.467–1.883)	0.86				
Hypertension	−0.201	0.301	0.818 (0.400–1.675)	0.58				
Diabetes mellitus	−0.145	0.154	0.865 (0.420–1.783)	0.70				
Follow-up period, yrs	0.006	0.003	1.006 (0.823–1.229)	0.96				
Clinical variable								
Spherical equivalence, D	−0.040	0.308	0.961 (0.835–1.106)	0.58				
Axial length, mm	−0.219	0.545	0.803 (0.449–1.437)	0.46				
Central corneal thickness, µm	−0.007	2.103	0.993 (0.983–1.003)	0.09	−0.005	0.992	0.995 (0.985–1.005)	0.32
Baseline IOP, mmHg	0.068	1.240	1.070 (0.950–1.205)	0.27				
Optic disc hemorrhage	0.880	4.691	2.410 (1.087–5.343)	0.030	**1.184**	**5.546**	**3.266 (1.220–8.747)**	**0.019**
Diagnosis of glaucoma	1.666	11.120	5.289 (1.987–14.079)	0.001	**2.499**	**5.585**	**12.167 (1.532–46.644)**	**0.017**
Optic nerve head parameter								
Baseline average CDR	0.314	2.849	1.369 (0.951–1.972)	0.091	0.146	0.296	1.158 (0.683–1.961)	0.59
Baseline vertical CDR	0.309	3.265	1.362 (0.974–1.905)	0.071				
Baseline disc area, mm^2	0.517	1.723	1.677 (0.775–3.628)	0.19				
Baseline rim area, mm^2	−0.446	0.357	0.640 (0.148–2.764)	0.55				

CDR = cup-to-disc ratio; CI = confidence interval; D = diopters; IOP = intraocular pressure; OR = odds ratio.
Values with statistical significance are shown in boldface.

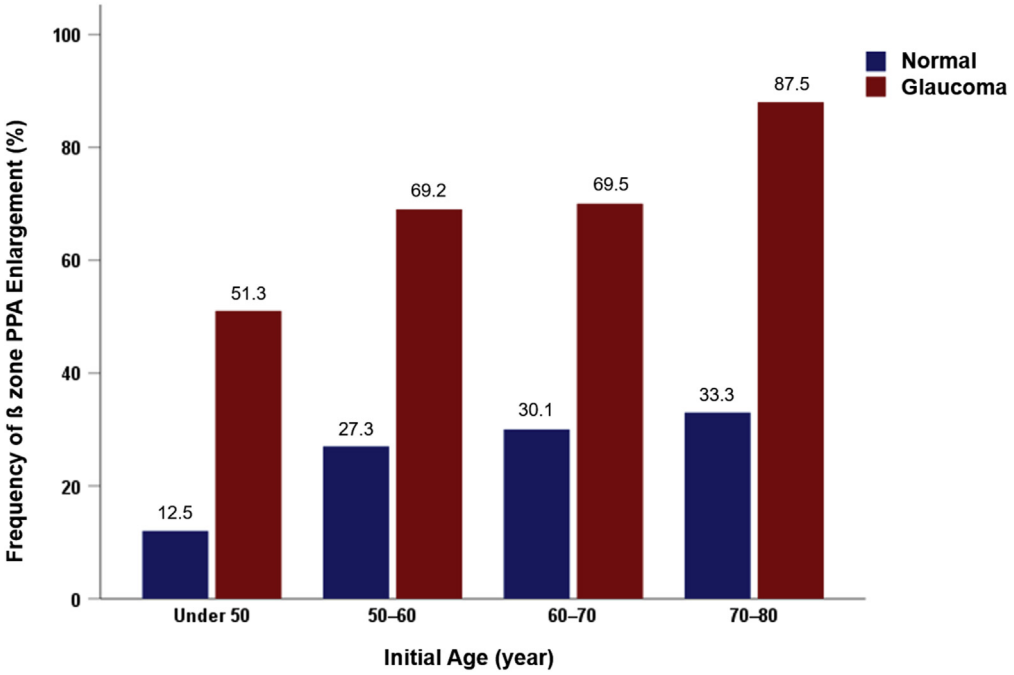

Figure 2. The frequency of ß-zone parapapillary atrophy (PPA) enlargement in the subgroups of initial age compared between the normal and primary open-angle glaucoma (POAG) subjects. The enlargement increased in older age. More frequent enlargement was detected in the older age groups, with marginal significance in normal eyes ($P = 0.20$) and statistical significance in POAG eyes ($P = 0.012$).

the increased vessel visibility, enlargement, or new development of a zone.[15,18,52]

Study Limitations

This study has several possible limitations. First, it was based on a single center, and all of the subjects were Koreans. These facts might have influenced the results, and certainly, the present findings might not pertain to other ethnic groups. Second, measurements were performed with disc photographs, which are flattened projections of the curved surface of the eye, and therefore, errors could have been incurred. Also, PPA was determined in a subjective manner, which could have resulted in a slight degree of measurement variability. However, because we required 3 repeated measurements between 2 masked reviewers, the inter-reader agreement for all of the PPA parameters was excellent. Third, myopic eyes were included in the analysis, and the reported prevalence of PPA is high in myopic eyes.[53,54] We endeavored to remove any effects of structural alterations on the optic nerve head accompanying axial elongation by excluding highly myopic eyes that could have shown different aspects of the optic disc such as a myopic crescent resembling PPA.[54] Our investigation of

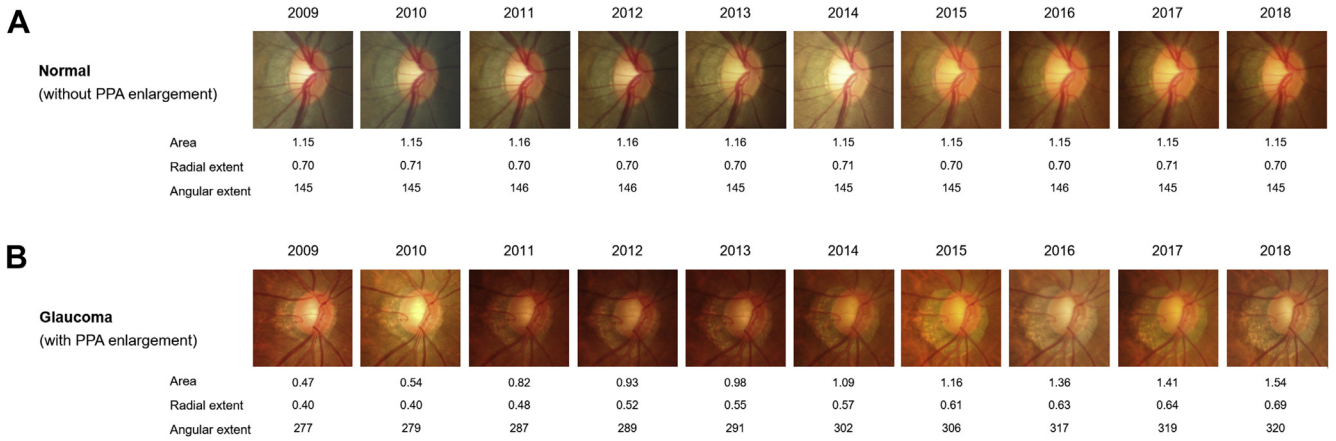

Figure 3. Serial examinations of representative comparative cases of (**A**) normal eye without ß-zone parapapillary atrophy (PPA) enlargement and (**B**) primary open-angle glaucoma (POAG) eye with ß-zone PPA enlargement. The first row in each figure shows serial disc photographs over the course of the 10-year follow-up period. The second row show shows the ß-zone PPA parameter values.

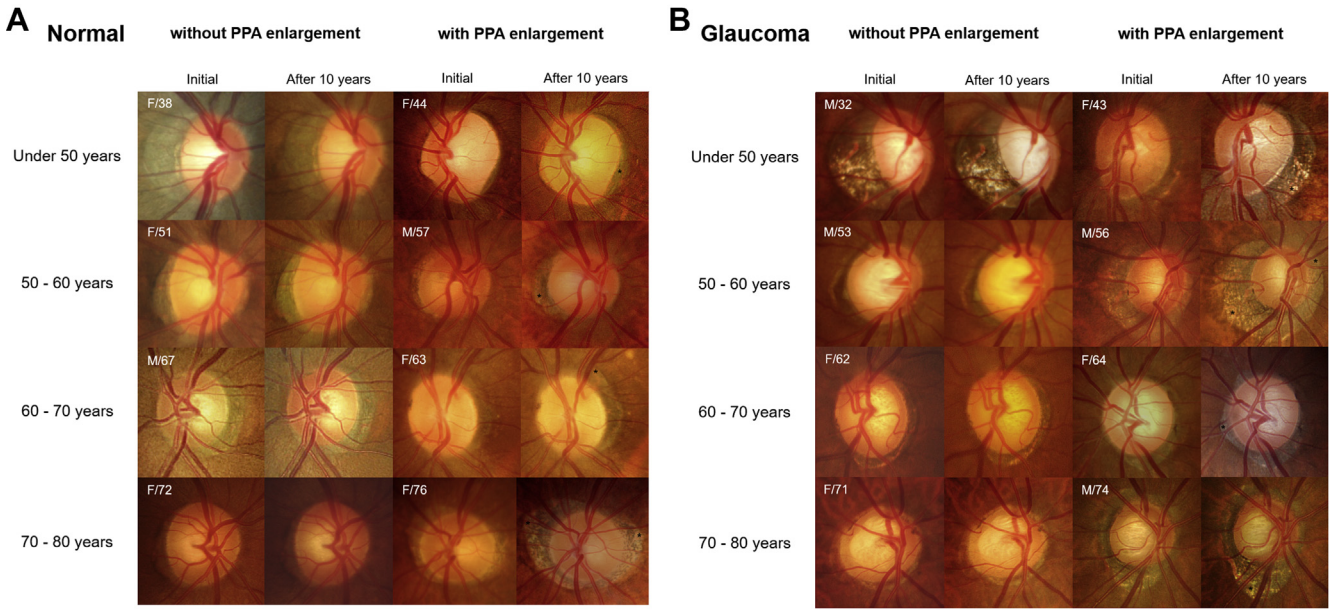

Figure 4. Representative disc photographs of ß-zone parapapillary atrophy (PPA) initially and after the 10-year follow-up period in (**A**) normal eyes and (**B**) primary open-angle glaucoma (POAG) eyes. The left 2 columns show cases without PPA enlargement, and the right 2 columns show cases with significant PPA enlargement. The 4 rows represent subgroups by initial age at first visit: first row, <50 years; second row, 50–60 years; third row, 60–70 years; and bottom row, 70–80 years. Note the enlargement in ß-zone PPA (**black asterisk**).

myopic refractive error in a univariate model of PPA enlargement did not show any relevant correlation. Regardless, caution needs to be exercised in generalizing our results. Fourth, contrary to the significant increment of circumferential extent of PPA in glaucomatous eyes, there was only a borderline difference between the glaucomatous and normal eyes at baseline (245.8° vs. 224.9°, $P = 0.049$). However, because the extent is associated with VF defects expressed in terms of MD,[12] the minimal baseline MD difference (−1.27 vs. −0.54 decibels) may reflect the borderline difference of circumferential extent. Further research with more severe stages of glaucoma is required. Fifth, our study was not ideally suited for distinguishing the microstructure of β-zone PPA, and only reliable OCT images were included to differentiate β-zone from γ-zone PPA. However, in our study population with an average myopic degree of only −0.86 D, all of the eyes presented OCT-defined β-zone PPA, whereas the prevalence of γ-zone PPA in glaucoma and normal eyes (34.3 vs. 32.9%) was similar to previous reports on mild myopia (30.1%).[55] The effect of myopia (known to be associated with γ-zone PPA) is assumed to be small, and the possibility of γ-zone presenting instead of β-zone PPA is relatively low. Further study investigating the microstructure of β-zone PPA with enhanced depth imaging is warranted.

In conclusion, over the course of 10 years or more of follow-up, the frequency of enlargement and pattern of β-zone PPA change differed between POAG and normal eyes. Widening of radial extent was associated with both older age and glaucoma, whereas circumferential increment of angular extent was related only to glaucomatous damage.

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Analysis and interpretation: Bak, Ha, Kim, Kim, Jeoung, Park

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Overall responsibility: Bak, Ha, Park

Abbreviations and Acronyms:
CI = confidence interval; **D** = diopters; **IOP** = intraocular pressure; **MD** = mean deviation; **OR** = odds ratio; **POAG** = primary open-angle glaucoma; **PPA** = parapapillary atrophy; **RNFL** = retinal nerve fiber layer; **RPE** = retinal pigment epithelium; **VF** = visual field.

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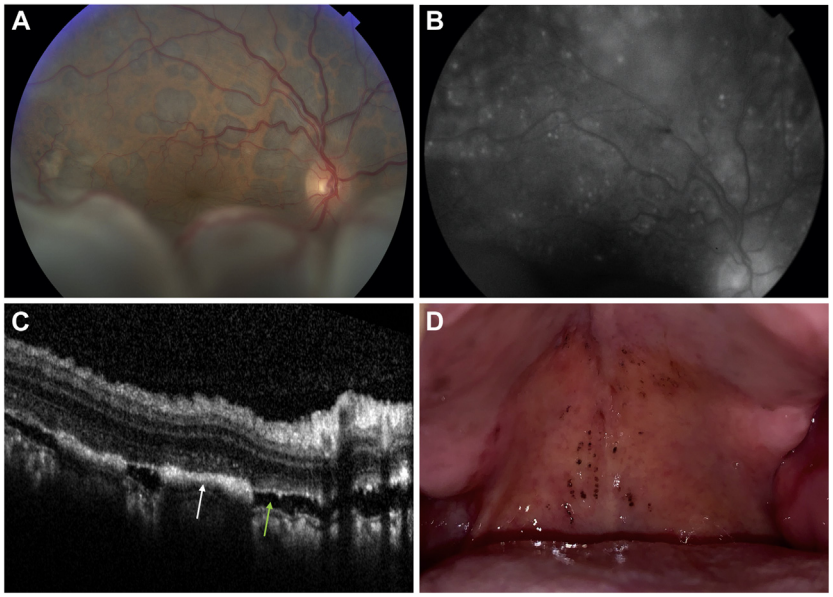
Pictures & Perspectives



Melanocytic Lesions in Buccal Mucosa in BDUMP

A 64-year-old woman with metastatic uterine carcinosarcoma presented with bilateral diffuse uveal melanocytic proliferation (BDUMP). Visual acuity was 20/400 and hand motions, respectively. Examination showed multiple subretinal oval grey patches with an inferior exudative retinal detachment (ERD) (Fig **A**) in the right eye, and a nearly complete ERD in the left. On fluorescein angiogram, multifocal areas of early hyperfluorescence were present (Fig **B**). OCT revealed hyperreflective areas (white arrow) in outer retina interspersed with regions of subretinal fluid (Fig **C,** green arrow). Numerous melanocytic lesions in buccal mucosa (Fig **D**), rarely seen in BDUMP, were observed. A careful review of the literature failed to reveal a previous report of these lesions in association with BDUMP in uterine carcinosarcoma. (Magnified version of Fig **A**-**D** is available online at www.aaojournal.org).

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