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Parapapillary gamma zone associated with increased peripapillary scleral bowing: the Beijing Eye Study 2011

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ABSTRACT

Aims To investigate the association between the backward configuration of the peripapillary sclera (PPS), measured as PPS angle (PPSA), and presence and extent of parapapillary gamma zone.

Methods Out of the population-based Beijing Eye Study 2011, we randomly selected individuals free of optic nerve and retinal diseases. With Spectralis optical coherence tomography, we measured gamma zone (zone free of Bruch's membrane (BM)) and determined the PPSA, defined as the angle between the anterior scleral surface lines from both sides of the optic nerve head (ONH).

Results The study included 678 individuals with age of 59.5±7.6 years (range: 50–90) and axial length of 23.5±1.3 mm (20.9–29.2). Gamma zone was more prevalent in eyes with larger PPSA (p=0.006) after adjustment for axial length (p<0.001) and BM opening area (p<0.001). Gamma zone width was positively associated with PPSA, axial length and BM opening area (all p<0.001) in multivariable analysis. Circular gamma zone was accompanied with larger PPSA as compared with focal gamma zone (19.9°±7.2° vs 6.3°±5.3°, p<0.001). Focal temporal gamma and focal inferior gamma had similar mean PPSA (p=0.69). However, the horizontal PPSA was significantly larger than the vertical PPSA in inferior gamma (6.9°±6.3° vs 4.7°±6.6°; p=0.005), while they were comparable in temporal gamma (6.1°±5.8° vs 6.3°±6.4°; p=0.073).

Conclusions A more backward bowing of the PPS was linearly and spatially associated with the presence, size and extent of gamma zone. It suggested that the BM and the sclera were closely related in participating the biomechanical behaviour of the ONH.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The presence of parapapillary gamma zone increased with older and myopic eyes, and may be related to the peripapillary scleral configuration and glaucomatous optic nerve damage.

WHAT THIS STUDY ADDS

⇒ A more backward bowing of the peripapillary sclera was linearly and spatially associated with the presence, size and extent of the gamma zone.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings should be helpful to further elucidate the biomechanics and pathogenesis in glaucoma and high myopia.

INTRODUCTION

The peripapillary sclera (PPS) consists of the posterior sclera splitting up into an inner part, which, as the peripapillary scleral flange, continues into the lamina cribrosa, and into an outer part which continues into the optic nerve dura mater.[1] The collagenous fibres of the peripapillary scleral flange, running in the coronary plane, are intertwined with the collagenous fibres of the peripapillary border tissue of the peripapillary scleral flange, which run in a sagittal direction and connect the optic nerve pia mater with the peripapillary border tissue of the choroid and eventually with the end of Bruch's membrane (BM).[2]

The peripapillary scleral flange in association with its border tissue forms the biomechanical anchor of the lamina cribrosa in sagittal and coronal direction.[3 4] Recent clinical studies, applying optical coherence tomography (OCT), have suggested that the PPS was increasingly backward bowed with older age and that this scleral backward bowing correlated with a thinner peripapillary choroid in healthy, non-highly myopic eyes.[5 6] The peripapillary scleral backward bowing was more pronounced in glaucomatous eyes than in non-glaucomatous ones.[7] It was discussed that the scleral backward bowing may mechanically contribute to, or may occur parallel to, an increased susceptibility to glaucomatous damage for the nerve fibres when passing through the lamina cribrosa.[7] Parapapillary gamma zone is the parapapillary region free of BM, where the scleral tissue is directly covered by the retinal nerve fibres, the elongated and thinned peripapillary choroidal border tissue of Jacoby, and the inner limiting membrane.[2 8] An increased prevalence of parapapillary gamma zone in older or myopic eyes was discussed to be related with the peripapillary scleral configuration and with glaucomatous optic nerve damage.[9]

Since gamma zone and the peripapillary scleral flange and sclera form integral parts of the anatomy of the optic nerve head (ONH), and since both, a large gamma zone and a backward bowing of the PPS, have been found to be associated with

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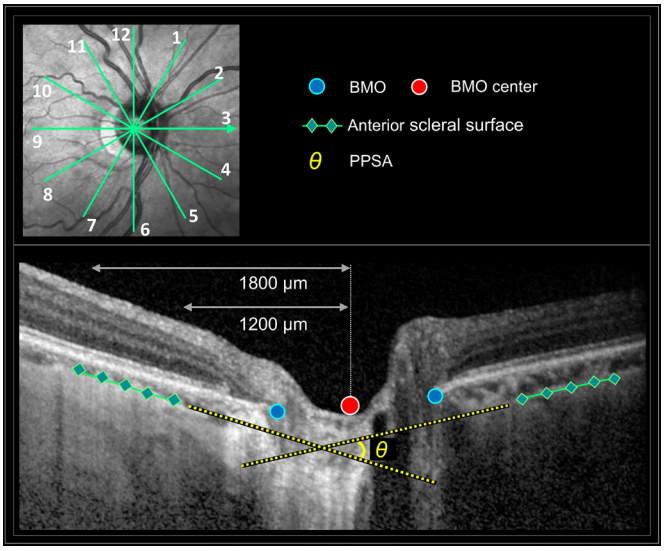

Figure 1 Illustration of the OCT scans of the optic nerve head and peripapillary scleral angle (PPSA) measurement. The upper infrared photograph of the optic nerve head shows the positions of the six radial scans; the lower image illustrated the PPSA measurement. PPSA was defined as the acute angle between lines drawn parallel to the anterior scleral surfaces at both sides of the optic nerve head. BMO, Bruch's membrane opening; OCT, optical coherence tomography.

glaucoma, we assessed in this study potential associations between gamma zone and the backward bowing of the PPS, in an attempt to get more information about the anatomy of the ONH.[1 4 10] The findings could be helpful to further elucidate the biomechanics of the ONH and the pathogenesis of glaucomatous optic neuropathy.

METHODS

The Beijing Eye Study 2011 is a population-based cross-sectional study conducted in northern China in the year 2011. It included 3468 individuals (1963 women, 56.6%) with a mean age of 64.6±9.8 years (range 50–93 years).[11 12]

Among 3234 (93.3%) participants with available OCT scans, we excluded those with the presence of any retinal disease or optic neuropathy, including any type of glaucoma, diabetic retinopathy, status after ocular trauma or retinal detachment, retinal vein occlusions, age-related macular degeneration and any other maculopathy; or participants with peripapillary choroidal cavitation or posterior staphyloma in the peripapillary area. Inclusion criterion was a best-corrected visual acuity (BCVA) of 20/25 or better for eyes with a refractive error (spherical equivalent) ranging between+1.0 and −4.00 D, and a BCVA of 20/33 or better for eyes with a refractive error of less than −4.00 D. We randomly selected 500 eyes and 50 eyes with the refraction within ±1.00 D and less than −1.00 to −2.00 D, respectively. All eyes with a refractive error of less than −2.00 D were enrolled.[12] Eyes with insufficient OCT image quality that did not allow the demarcation of anatomical landmarks in at least one radial B scan were also furtherly excluded.

All study participants underwent spectral-domain OCT of the ONH applying the enhanced depth imaging modality (Spectralis; Heidelberg Engineering, Heidelberg, Germany), centred on the optic disc. The ONH imaging pattern consisted of 6 radial B-scans (30°apart with each B scan comprising 512 A-scans), with an average of 100 repetitions each. Using the intrinsic viewer (Heidelberg Eye Explorer software V.1.7.0.0; Heidelberg Engineering), two trained ophthalmologists (CCX and QZ), independently of each other, determined the presence of gamma zone and measured its width in the six radial B scans. The images were examined with a magnification of up to 200%. In eyes in which the end of BM did not reach the optic disc border, we measured the distance between the end of BM and the optic disc border, defined by the end of the lamina cribrosa and/or the peripapillary border tissue of the peripapillary scleral flange. The length of an absence of BM had to be ≥100 µm on at least one radial B scan image to fulfil the definition of gamma zone.[13] Gamma zone width was defined as the length on the B scan without BM. Circular gamma zone (c-gamma) was defined if gamma zone was present at both disc sides in the same radial B scan (ie, independently, whether gamma zone was additionally present in the superior region and/or in the inferior region).The remaining eyes with a gamma zone (ie, focal gamma zone) were stratified into those with a temporal gamma zone (t-Gamma), inferior gamma zone (i-Gamma), nasal gamma zone and superior gamma zone, according to the location of the maximal gamma zone width.

The raw OCT images were postprocessed and enhanced using adaptive compensation to reduce blood vessel shadows and to improve the visibility of the lamina cribrosa and the anterior scleral surface, as previously described.[14] The labelling and measurements were performed, using the custom-written MATLAB (MathWorks, Natick, Massachusetts, USA) algorithms.

Two trained examiners (CCX and YXH) were responsible for delineating the anatomic landmarks in each of the six OCT radial B-scans, including the BM opening (BMO), the anterior lamina cribrosa surface, the posterior surface of the BM and the anterior scleral surface.

The peripapillary scleral angle (PPSA) was defined as the angle between the two anterior scleral surfaces lines from both sides of the ONH, locating at a distance from 1200 μm to 1800 µm away from the BMO centre (figure 1). A negative value suggests an inverted V-shaped configuration of the PPS, while a positive value indicated a V-shaped configuration.[5] The PPSA was measured in six radial B-scans, with 30° apart from each other. The horizontal-vertical PPSA difference was defined as the horizontal PPSA (OCT scan from 9 o'clock to 3 o'clock position) minus the vertical PPSA (OCT scan from 6 o'clock to 12 o'clock position).

The lamina cribrosa depth was measured as the average perpendicular distance between the anterior lamina cribrosa surface and the BMO reference plane within the one-third central region in the BMO.[15] The peripapillary choroidal thickness was measured as the mean thickness within the region of 1200–1800 µm from the BMO centre.[5] The measurement of the optic disc-fovea angle, defined as the angle between the optic disc-fovea line and the horizontal, was performed on fundus photographs.[16]

The interobserver reproducibility in OCT image delineation between two graders was assessed in images from 100 randomly selected B scan images.

Statistical analyses were performed using a software program (SPSS V.27.0; SPSS). We assessed the associations between the PPSA and other variables first in univariable linear regression analyses, followed by a stepwise multivariable linear regression analysis. To investigate the factors associated with the presence of gamma zone, binary logistic regression analyses were performed, first in a univariable mode, followed by a stepwise multivariable analysis with the presence of gamma zone as the dependent variable and all those parameters as independent variables which were significantly associated with the gamma zone

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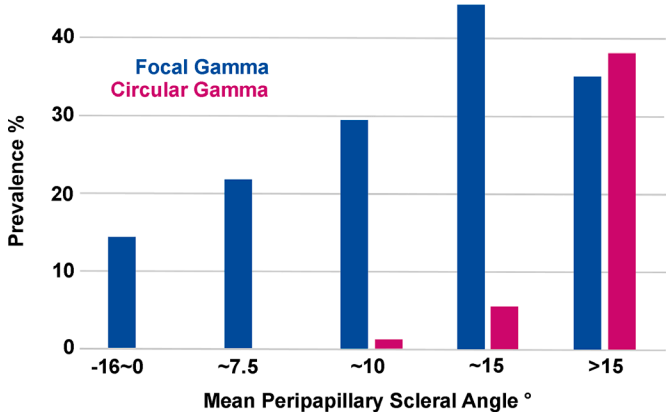

Figure 2 The prevalence of focal gamma zone and circular gamma zone (c-Gamma) in eyes with varied peripapillary scleral angle (PPSA). The prevalence of both focal gamma zone and c-Gamma increases with PPSA, note that the c-Gamma only exist in eyes with a PPSA larger than 7.5°, and even surpassed the prevalence of focal gamma zone in those with a PPSA higher than 15°.

presence (p<0.05) in the univariable analysis. We additionally compared the PPSA and its horizontal-vertical ratio between eyes with c-Gamma, i-Gamma and t-Gamma, using an analysis of variance for continuous variables and χ^2 test for categorical variables. For all multiple analyses, the variance inflation factor was calculated to estimate the collinearity. A two-tailed p<0.05 was considered to be statistically significant.

RESULTS

The study included 678 eyes from 678 individuals (400 women, 59.0%) with a mean age of 59.5±7.6 (range 50–90 years) years and a mean axial length of 23.5±1.3 mm (range 20.9–29.2 mm), after excluding 37 eyes due to low-quality OCT images. The excluded individuals as compared with the participants included had a significantly older age (63.0±8.9 vs 59.5±7.6, p=0.024) and longer axial length (26.0±2.4 vs 23.5±1.3, p<0.001).

Gamma zone

Gamma zone was detected in 180 eyes, with a prevalence of 26.5% (95% CI:23.3% to 29.9%). Mean maximum width of gamma zone was 328±200 µm (range: 103–1103 µm). The presence and width of gamma zone increased with increasing myopic refractive error (p<0.001). C-Gamma and focal gamma zone were found in 17 eyes (9.4%) and 163 (90.6%) eyes, respectively. Focal gamma zone was further stratified into t-Gamma (86 eyes, 47.8%), i-Gamma (67 eyes, 37.2%) and gamma zone located either superiorly or nasally (10 eyes, 5.6%) (online supplemental table 1).

PPSA with prevalence and width of gamma zone

The mean PPSA was 4.8°±5.4° (median 4.1°; range −7.2° to 37.7°). Demographics and ocular associations of mean PPSA are shown in online supplemental table 2. The mean PPSA was significantly larger in eyes with gamma zone than in eyes without gamma zone (7.6°±6.8° vs 3.8°±4.4°; p<0.001) in univariate analysis. After adjusting for demographic and ocular parameters (ie, age, sex, axial length, BMO area, lamina cribrosa depth and peripapillary choroidal thickness), the mean PPSA remained to be significantly related to the presence of gamma zone (p=0.006, OR:1.06) (table 1) (figure 2). In a parallel manner, a positive association was found between the gamma zone width and the mean PPSA (p<0.001, coefficient B: 4.96; 95% CI 2.96 to 6.96) after adjustment for axial length (p<0.001), BMO area (p<0.001) and age (p=0.93).

PPSA with subtypes of gamma zone

In the next step of the statistical analysis, the PPSA and its associations were compared between the subtypes of gamma zone (table 2).

In comparison with focal gamma zones (t-Gamma or i-Gamma), the presence of c-Gamma was associated with older age, a more myopic refractive error, longer axial length, larger gamma zone width, larger BMO area, thinner peripapillary choroid, larger optic disc-fovea angle, higher PPSA in each B scan (all p<0.05) and higher mean PPSA (19.9°±7.2° vs 6.3°±5.3°, p<0.001), in univariable analysis (table 2, figure 2). A higher mean PPSA remained to be significantly associated with the presence of c-Gamma in the multivariable model (p=0.001, OR 1.37; 95% CI 1.14 to 1.65) (figure 3).

The mean PPSA did not differ significantly between t-Gamma group and i-Gamma group (6.4°±4.9° vs 6.1°±5.5°; p=0.69) (table 2). Interestingly, the horizontal PPSA was significantly larger than the vertical PPSA (6.9°±6.3° vs 4.7°±6.6°; p=0.005) in eyes with i-Gamma, while the horizontal and the vertical PPSA did not differ significantly (6.1°±5.8° vs 6.3°±6.4°; p=0.73) in eyes with t-Gamma. Correspondingly, the horizontal-vertical PPSA difference was smaller in eyes with t-Gamma than in eyes with i-Gamma (−0.2°±6.4° vs 2.3°±6.2°; p=0.010), and the

Table 1 Factors associated with the presence of gamma zone, by comparing the group with gamma zone and the group without gamma zone, in univariate and multivariate analysis

	Gamma zone	Without gamma zone	Univariable analysis		Multivariable analysis	
	(n=180)	(n=498)	P value	OR (95% CI)	P value	OR (95% CI)
Age (years)	61.2±7.8	58.9±7.4	<0.001	1.04 (1.02 to 1.06)	0.67	0.99 (0.96 to 1.03)
Gender (male/%)	99/55.0	179/35.9	<0.001	2.18 (1.54 to 3.08)	0.11	1.42 (0.92 to 2.20)
IOP (mm Hg)	14.9±2.8	14.5±2.5	0.08	1.06 (0.99 to 1.13)	/	
Axial length (mm)	24.5±1.5	23.2±0.9	<0.001	2.51 (2.11 to 3.0)	<0.001	2.33 (1.91 to 2.83)
BMO area (mm^2)	2.5±0.6	2.2±0.4	<0.001	4.52 (2.98 to 6.87)	<0.001	3.52 (2.11 to 5.88)
PCT (µm)	123±37	138±40	<0.001	0.99 (0.98 to 0.995)	0.10	0.99 (0.99 to 1.00)
LC depth (µm)	446±99	450±101	0.66	0.99 (0.99 to 1.001)	0.07	1.00 (1.00 to 1.01)
PPSA (°)	7.6±6.8	3.8±4.4	<0.001	1.14 (1.10 to 1.18)	0.006	1.06 (1.02 to 1.11)

All variables included in the multivariable model with their VIF less than 1.53.
BMO, Bruch's membrane opening; IOP, intraocular pressure; LC, lamina cribrosa; PCT, peripapillary choroidal thickness; PPSA, peripapillary scleral angle; VIF, variance inflation factor.

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Table 2 Univariable comparison of clinical and ocular characteristics among circular gamma (c-Gamma), temporal gamma (t-Gamma) and inferior gamma zone (i-Gamma)

					Comparison between two groups		
	i-Gamma (n=67)	t-Gamma (n=86)	c-Gamma (n=17)	Comparison among three groups*	i-Gamma versus t-Gamma	i-Gamma versus c-Gamma	t-Gamma versus c-Gamma
Age (years)	60±6.3	61.0±7.8	68.7±9.3	0.003	0.37	0.002	<0.001
Sex (male/%)	29/43.3	56/65.1	8/47.1	0.021	0.007	0.779	0.161
Axial length (mm)	24.2±1.4	24.7±1.4	26.3±1.3	<0.001	0.04	<0.001	0.001
Refractive error (diopter)	−2.4±2.6	−3.0±3.2	−5.8±3.9	<0.001	0.16	<0.001	0.002
IOP (mm Hg)	14.9±2.9	15.3±2.8	14.0±2.9	0.24	0.48	0.24	0.093
BMO area (mm^2)	2.4±0.4	2.4±0.5	3.2±1.0	0.01	0.97	0.006	0.006
Disc-fovea angle (°)	8.9±4.1	6.3±3.4	10.7±4.0	<0.001	<0.001	0.23	0.001
PCT (µm)	125±30	126±42	92±20	<0.001	0.77	<0.001	<0.001
LC depth (µm)	455±78	439±107	417±123	0.33	0.27	0.24	0.46
PPSA 7–1 (°)	6.1±6.1	6.3±5.5	18.1±7.0	<0.001	0.79	<0.001	<0.001
PPSA 8–2 (°)	6.6±4.8	6.0±5.8	17.1±8.1	<0.001	0.51	<0.001	<0.001
PPSA 9–3 (°)†	6.9±6.3	6.1±5.8	18.1±8.1	<0.001	0.39	<0.001	<0.001
PPSA 10–4 (°)	6.5±6.5	7.0±5.1	24.4±8.9	<0.001	0.59	<0.001	<0.001
PPSA 11–5 (°)	5.8±7.0	6.7±6.6	21.7±9.6	<0.001	0.42	<0.001	<0.001
PPSA 6–12 (°)‡	4.7±6.6	6.3±6.4	20.0±8.6	<0.001	0.13	<0.001	<0.001
Mean PPSA (°)	6.1±5.5	6.4±4.9	19.9±7.2	<0.001	0.69	<0.001	<0.001
Gamma zone width (µm)	308±164	301±185	618±226	<0.001	0.8	<0.001	<0.001

PPSA 7–1 represents the PPSA at the scan starting from 7 o'clock to 1 o'clock. Similar for PPSA 8–2, 9–3, 10–4, 11–5 and 6–12.
*For comparison among eyes with i-Gamma, t-Gamma and c-Gamma, one-way ANOVA was used for the continuous variables while χ^2 test was used for the categorical variables.
†The PPSA 9–3 is the horizontal PPSA.
‡The PPSA 6–12 is the vertical PPSA.
ANOVA, analysis of variance; BMO, Bruch's membrane opening; IOP, intraocular pressure; LC, lamina cribrosa; PCT, peripapillary choroidal thickness; PPSA, peripapillary scleral angle.

difference between the two groups remained to be significant (OR 0.93; 95%CI 0.87 to 0.99; p=0.04) after adjusting for sex (p=0.053), axial length (p=0.04), BMO area (p=0.94) and optic disc-fovea angle (p<0.001) (figure 3).

Interobserver repeatability

The measurement of maximum gamma width, BMO area, lamina cribrosa depth, peripapillary choroidal thickness and PPSA all showed good interobserver repeatability, with the intraclass correlation coefficients ranging from 0.90 (95% CI 0.87 to 0.92) to 0.99 (95% CI 0.985 to 0.992).

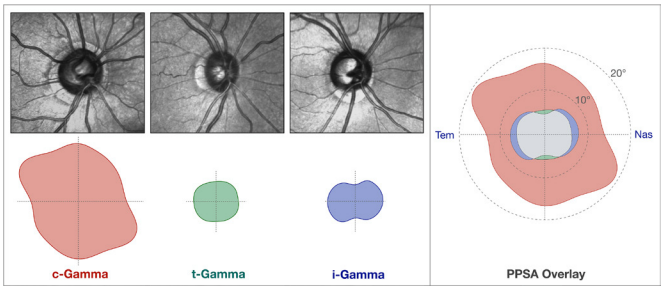

Figure 3 Illustration of the gamma zone and the topographic distribution of peripapillary scleral angle (PPSA) in each type of gamma zone, with age- and axial length-standardisation. The left images show the age-standardised and axial length-standardised PPSA, for circular gamma zone (c-Gamma), temporal gamma zone (t-Gamma) and inferior gamma zone (i-Gamma), respectively. The distance from the centre to the coloured area's border indicates the extent of PPSA at the same direction. The larger the distance, the higher the PPSA. The right image shows the overlay of the PPSA in eyes with c-Gamma, i-Gamma and t-Gamma. PPSA in c-Gamma (red) was significantly higher than PPSA in t-Gamma (green) or in i-Gamma (blue) in each direction; The horizontal PPSA was significantly higher than the vertical PPSA in i-Gamma, while they were comparable in t-Gamma.

DISCUSSION

In our population-based study including eyes without retinal or optic nerve diseases, the occurrence and extent of parapapillary gamma zone was associated with the size and regional distribution of the PPSA, that is, with the amount of backward bowing of the PPS, after adjusting for parameters such as age, axial length and BMO size. Correspondingly, the PPSA correlated with the type of gamma zone, being larger in eyes with a c-Gamma than in eyes with a focal gamma zone. While the PPSA did not differ significantly between eyes with an i-Gamma and eyes with a t-Gamma, the horizontal-to-vertical PPSA difference was higher in eyes with i-Gamma.

The observations made in our study agree with findings obtained in previous study samples, such as the association between a larger (ie, steeper) PPSA with older age,[5 6] and additionally with longer axial length and a deeper lamina cribrosa.[5] In contrast to previous studies such as the one performed by Tun *et al*, our study did not reveal a correlation between the PPSA and the peripapillary choroidal thickness in the multivariable model. The discrepancy between this study and Tun's investigation may be due to differences in the OCT scans, as Tun *et al* used a single horizontal radial B scan to assess the PPSA, instead of the radial scans examined in this study.[5] Wang *et al* examined a hospital-based recruited, multiethnic study population with a wider age range instead of our study population consisting of Chinese with a smaller age range.[6] Age and ethnic background may be confounding factors, since the biomechanical properties of the sclera depend on both parameters.[17 18] The association between gamma zone and a longer axial length and a larger BMO as found in this study is consistent with previous reports by others and findings from other groups.[12 19 20] The novel finding

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obtained in this study was that an increasing PPSA was linearly and spatially associated with the presence, shape and extent of gamma zone.

The spatial association between gamma zone and a steeper PPSA, as newly described in our study population, raises the question on a potential causal relationship between gamma zone, defined as and characterised by the absence of BM, and a local backward configuration of the sclera. Previous histological and clinical studies have addressed the potential role of BM in the biomechanics of the eye in general and its potential role in the process of axial elongation in particular.[21 22] These studies revealed that the thickness of BM, in contrast to the thickness of the posterior scleral and choroid, did not decrease with longer axial length, so that BM in the macular region, and in any other regions of the eye, was in highly myopic eyes as thick as it was in emmetropic eyes.[23] With BM thickness being independent of axial length, the axial elongation-associated increase in the BM surface area indicated an increase in BM volume. In contrast, the volumes of the choroid and sclera were not independent of axial.[24] Myopic axial elongation leads to a change from a spherical eye shape in emmetropia to a prolate ellipsoid in myopia.[25] Geometric reasons and measurements of the regional density of photoreceptors and retinal pigment epithelium cells suggested that the ocular wall enlargement, occurring in association with the axial elongation, predominantly occurred in the retroequatorial and equatorial region.[26 27] A potential enlargement of BM most markedly in the retroequatorial and equatorial region would push the posterior BM backward, explaining the marked thinning of the posterior choroid, while the thinning of the posterior sclera would occur secondarily.[28] If, as an alternative mechanism, myopic eye elongation primarily occurred through a scleral extension, the thickness of the posterior choroid would increase since the posterior sclera would move backward.[21] Fitting with the notion of BM as a biomechanical important structure are findings, that the biomechanical strength of BM, in relationship to the tissue thickness, is about 100 times higher than that of the sclera; that non-highly myopic eyes with an acquired defect in BM, such as in association with a toxoplasmotic scar, show a localised scleral staphyloma; and that eyes with congenital BM defects in association with a coloboma also show a collateral scleral staphyloma; and that highly myopic eyes with a scleral staphyloma have BM defects in the vicinity of the staphyloma.[29–31] The findings described above fit with the observation that gamma zone, or the absence of BM, is associated with a localised backward configuration of the PPS. It agrees with the notion of BM as a biomechanical important structure supporting form and shape of the eye.[21]

The association between the absence of BM (ie, gamma zone) and the backward configuration of the PPS is supported by the finding that eyes with c-Gamma as compared with eyes with a focal gamma zone had a more pronounced backward configuration. The notion is also strengthened by the observation that the width of gamma zone was linearly correlated with the amount of the PPSA, after adjusting for other parameters such as axial length, BMO area and age. The notion is further supported by a spatial association between the location of gamma zone and the location of the most marked backward formation of the PPS. In eyes with an i-Gamma, the PPSA was significantly larger in the horizontal axis than in the vertical axis, while in eyes with a t-Gamma, the PPSA was similar in the vertical axis and in the horizontal axis. Correspondingly, eyes with t-Gamma as compared with eyes with an i-Gamma had a significantly lower horizontal-to-vertical PPSA difference.

Besides BM, the peripapillary choroidal border tissue (of Jacoby) is another anatomical structure of interest for the biomechanics of the ONH and of the eye. It connects the peripapillary end of BM with the peripapillary scleral flange border tissue, which continues into the optic nerve pia mater.[2] In eyes with gamma zone, the distance between BM end and the optic disc border is enlarged, that is, the choroidal peripapillary border tissue gets elongated and secondarily thinned.[2] One may discuss that lengthening and secondary thinning of the choroidal peripapillary border tissue may lead to a reduction of its biomechanical strength, so that besides the absence of BM, these gamma zone-associated changes in the choroidal peripapillary border tissue may be another cause for the backward configuration of the PPS in eyes with gamma zone.

In highly myopic eyes, an additional force may come into play. Recent studies by Demer, Wang and others have indicated that optic nerve may get too short to allow a full adduction of the globe in axially elongated, highly myopic eyes.[32 33] It may lead to a force pulling backward the peripheral end of the peripapillary scleral flange, which is the insertion line of the optic nerve dura mater with the posterior sclera.[1] It has been discussed that such a force may be the reason for the development of peripapillary suprachoroidal cavitations which are characterised by a cleavage between the PPS and the choroid, which remains attached to BM.[34 35] An argument in favour of this hypothesis is the location of the cavitations usually located at the inferior and temporal inferior border of the ONH. That location is the region of the ONH most distant to the orbital origin of the optic nerve which enters the orbit in the nasal upper region of the orbit. A peripapillary suprachoroidal cavitation may be considered as an extreme form of a marked PPSA. In that context, a peripapillary scleral staphyloma may also be considered as an extreme form of a large PPSA.

The deformation and stress conditions of the ONH in response to intraocular pressure are strongly influenced by the material properties and biomechanical behaviour of the PPS. Ma *et al* explored the regional displacements in the human ONH and peripapillary tissue in response to acute intraocular pressure elevations and found that a thinner PPS was associated with a larger relative backward movement of the ONH.[36] Midgett *et al* investigated the inflation response of the lamina cribrosa and adjacent PPS in human donor eyes without a history of glaucoma and described that a stiffer pressure-strain response of the PPS was associated with a greater posterior bowing of the lamina cribrsosa.[37] Coudrillier *et al* reported that PPS stiffening was effective in reducing the magnitude of biomechanical strains within the lamina cribrosa.[38] These observations suggest that development and characteristics of gamma zone were paralleled by the biomechanical deformation of the PPS.

Questions regarding whether there is a causal relationship between a larger PPSA and the presence of a gamma zone remain elusive so far. However, since the ONH responds to intraocular pressure elevation and fluctuation as a structural system,[39] the geometry and the material properties of PPS directly influence the ONH biomechanics.[40]

The clinical meaning of the association between a steeper PPSA and a higher prevalence and larger width of gamma zone as novel observations made in this study is yet unclear. In view of the relatively small difference in the amount of the PPSA between eyes without vs with gamma zone, the finding may be more interesting with respect to the aetiology of gamma zone and anatomical and biomechanical aspects of the ONH than with respect to a clinical application. Future clinical studies may address in particular the PPSA in highly myopic eyes, including those with a peripapillary suprachoroidal cavitation, and its

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relationship with gamma zone and other anatomical landmarks of the ONH.

The limitations of our study should be discussed. First, although the Beijing Eye Study is a population-based investigation, the population of this study was selected based on the absence of optic nerve and retinal diseases. This selection might have introduced a bias. However, it was not the primary goal of the study to assess the prevalence of gamma zone and the mean PPSA in a population but to explore associations of the PPSA. Second, in a similar manner, the Beijing Eye Study consisted of Chinese, so that the results of this study may not directly be transferred to other ethnicities.

In conclusion, an enlarging PPSA, that is, a more backward bowing of the PPS, was linearly and spatially associated with the presence, shape and extent of gamma zone, that is, with an absence of BM in the parapapillary region. It suggested that the BM and the sclera were closely related in participating the biomechanical behaviour of the ONH.

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Supplemental Table 1. Prevalence of gamma zone in the study participants stratified by refractive error

Refractive error (diopters (D))	n	Any gamma zone		*c-Gamma*		Focal gamma zone		*i-Gamma**		*t-Gamma**	
		n	% (95%CI)	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)
Emmetropia/ Hyperopia (>-0.5D)	388	52	13.4 (10.3, 16.8)	1	0.3 (0.1, 0.5)	51	13.1 (10.1, 16.6)	19	4.9 (3.3, 6.8)	23	5.9 (4.1, 8.1)
Mild Myopia (-2.99 D to -0.50D)	166	42	25.3 (19.0, 32.2)	1	0.6 (0.1, 1.4)	41	24.7 (18.5, 31.5)	20	12.0 (7.7, 17.2)	20	12.0 (7.7, 17.2)
Moderate Myopia (-5.99 D to -3.00 D)	73	46	63.0 (56.8, 69.0)	6	8.2 (3.4, 14.8)	40	54.8 (46.3, 63.2)	13	17.8 (10.0, 27.3)	27	37.0 (26.8 ,47.7)
High Myopia (≤ -6.00 D)	51	40	78.4 (NA)	9	17.6 (8.6, 29.1)	31	60.8 (52.4, 68.8)	15	29.4 (17.9, 42.4)	16	31.4 (19.7, 44.4)

*included in focal gamma group
CI: confidence interval; *i-Gamma*: inferior gamma zone; *t-Gamma*: temporal gamma zone; *c-Gamma*: circular gamma zone

Supplemental Table 2. Factors associated with the mean peripapillary scleral angle

	Univariable analysis		Multivariable analysis	
	Coefficient B	*P*	Coefficient B	*P*
Age (years)	0.220	0.000	0.178	<0.001
Female	-0.795	0.059	0.560	0.144
IOP (mmHg)	0.021	0.794	/	/
Axial length (mm)	1.285	0.000	1.026	<0.001
Central cornea thickness (μm)	0.016	0.010	0.012	0.036
Cornea curvature	0.645	0.411		
BMO area (mm^2)	2.674	0.000	1.314	0.001
LC depth (μm)	0.004	0.085	0.008	<0.001
PCT (μm)	-0.008	0.137	/	/

IOP: intraocular pressure; BMO: Bruch´s membrane opening; LC: lamina cribrosa; PCT: Peripapillary choroidal thickness;All variables included in the multivariable model with their VIF less than 1.13.