• Clinical Research •

Ultrasound biomicroscopic imaging demonstrate thinner ciliary body thickness in eyes with angle closure

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Abstract

● **AIM:** To compare the ciliary body thickness between eyes with primary angle closure (PAC) and primary angle-closure glaucoma (PACG) with the normal eyes, and to investigate the association between ciliary body thickness and ciliary processes situation.

● **METHODS:** In this cross-sectional study, 57 patients with PAC/PACG were matched to 57 normal subjects after propensity score matching (PSM) adjusting for age and gender. All subjects underwent conventional ocular examinations and ultrasound biomicroscopy (UBM) examination, among which the patients with PAC/PACG performed the examinations one month after laser peripheral iridotomy (LPI). Quantitative parameters were measured, which included ciliary body thickness at the position of 1 mm posterior to the scleral spur (CBT1), trabecular-ciliary process distance (TCPD) and trabecular-ciliary process angle (TCA).

● **RESULTS:** Eyes with PAC/PACG presented significantly thinner CBT1, shorter TCPD and smaller TCA (P<0.001) than the normal eyes, both in comparison of the means of four quadrants and in comparisons of each quadrant. After removing images with peripheral anterior synechia (PAS), the same results were also found in comparisons between the two groups. Significant correlations were found between TCPD (R^2=0.537, P<0.001) and TCA (R^2=0.517, P<0.001) with CBT1.

● **CONCLUSION:** Eyes with PAC/PACG have thinner ciliary body thickness and more anteriorly situated ciliary processes. Thinner ciliary body thickness is associated with anterior situation of the ciliary processes.

● **KEYWORDS:** glaucoma; angle closure; ciliary body; ultrasound biomicroscopy
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INTRODUCTION

Angle closure has been proved to be associated with specific anatomic features of the globe. Compared with normal eyes, eyes with primary angle closure (PAC) and primary angle-closure glaucoma (PACG) present biometric features of shallow anterior chamber depth, narrow angle, short axial length, thick lens and anterior lens position[1-2]. Moreover, eyes with specific peripheral iris configuration, such as plateau iris, thick iris and anteriorly inserted iris, are also associated with angle closure, including appositional angle closure after laser peripheral iridotomy (LPI)[3].

Ciliary body is one of the important parts of the angle, and the biometric features of the ciliary body were proved to be related with angle closure as well. Previous studies have revealed that anterior situation of the ciliary processes is a predisposing factor of PAC/PACG[2,4-5]. The anteriorly situated ciliary processes are thought to be the main cause of plateau iris by pushing the iris root toward the trabecular meshwork[6], and may induce thick lens and anterior lens position through loosening the zonules as well[7-8].

Ciliary body thickness is supposed to be another potential factor for angle closure[7-11]. Gohdo *et al*[7] first found thinner ciliary body thickness in eyes with gonioscopic narrow but open angle (Shaffer classification, grade 0 to 2). Then similar results were also found in eyes with some special kinds of angle-closure glaucoma: thinner ciliary body thickness was found in eyes with acute primary angle closure (APAC)[9-10],

and also in eyes with malignant glaucoma[11]. However, there were no definite results yet about the ciliary body thickness in eyes with PAC/PACG compared to the normal ones.

Our previous work found that the Chinese ethnic had thinner ciliary body and more anteriorly positioned ciliary processes than the Caucasians[8], which was consistent with the higher prevalence of angle closure in Chinese population. To further investigate the effect of ciliary body thickness on eyes with angle closure, this ultrasound biomicroscopy (UBM) study was carried out to quantitatively compare the ciliary body configuration between eyes with PAC/PACG and the normal eyes.

SUBJECTS AND METHODS

Ethical Approval The study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Peking University Third Hospital. Signed informed consent was obtained from each subject involved in this study.

This was a cross-sectional comparative study consisting of two groups: PAC/PACG patients and normal subjects. This study was performed at the Peking University Third Hospital, Peking University Eye Centre by 5 clinicians, including 2 full-time attending glaucoma specialists (Wu LL, Fan X) and 3 glaucoma fellows (Chen SY, He N, Yan YJ). Patients with PAC/PACG were consecutively enrolled in this study who underwent LPI at the glaucoma clinic of Peking University Third Hospital between January 2009 and December 2009. The inclusion criteria included: 1) age between 40 and 80y; 2) conformed to the diagnostic criteria of PAC/PACG. The diagnostic criteria of PAC were defined as follows[12]: an eye with an occludable drainage angle (an angle in which ≥270 degree of the posterior trabecular meshwork could not be seen with static gonioscopy) and features that indicated trabecular obstruction by the peripheral iris had occurred, such as peripheral anterior synechia (PAS), elevated intraocular pressure (IOP), or excessive pigment deposition on the trabecular surface, and without glaucomatous damage to the optic disc. While PACG was defined as presence of glaucomatous optic neuropathy (such as loss of neuroretinal rim with a vertical cup-to-disc ratio of >0.7 and/or notching with nerve fibre layer defect) with corresponding visual field loss on the basis of the diagnosis of PAC. Patients were excluded if any of the following conditions present: 1) secondary angle closure, such as neovascularization of the iris, uveitis, trauma, tumour, lens intumescence or subluxation; 2) any other ocular diseases (except for mild cataracts and refractive error with the spherical equivalent within -8 D and 4 D) or previous intraocular surgery; 3) unable to perform contact examination such as gonioscopy or UBM; 4) sustained pilocarpine or prostaglandin administration which might affect ciliary body morphology[13]; 5) eyes with more than two quadrants of PAS and uncontrolled IOP with medications, which indicated for the filtration surgery; 6) acute attack history which might lead obvious uveal effusion[14] or pupil distortion and iris whirling.

Normal control subjects were consecutively recruited from general ophthalmologic clinic of Peking University Third Hospital between January 2009 and December 2009. The inclusion criteria for normal subjects included: 1) age between 40 and 80y; 2) willing and capable to attend this study. And one was excluded if presenting any intraocular diseases (including PAC/PACG, except for mild cataracts and refractive error with the spherical equivalent within -8 D and 4 D), or having previous intraocular surgery or laser treatment history, or any other condition conforming to the exclusion criteria for the PAC/PACG group.

All subjects underwent comprehensive ocular examinations, including best-corrected visual acuity, IOP measurement by Goldmann applanation tonometry, slit-lamp biomicroscopy, direct ophthalmoscopy, static and dynamic gonioscopy, and UBM examination. For patients with PAC/PACG, all of the ocular examinations were performed one month after LPI. IOP record of the eyes studied was measured just before the UBM examination. Gonioscopy was performed in dark environment using a Goldmann single-mirror gonioscopy lens. Part of the eyes with PAC/PACG were under treatment with IOP-lowering medications (except prostaglandin), but administration of pilocarpine was discontinued for two weeks or more.

Ultrasound Biomicroscopy UBM examination was performed with a UBM (model P45, Paradigm Medical, Salt Lake City, UT, USA) equipped with a 50-MHz transducer probe allowing 5.0×5.0 mm^2 field of view and approximately 50 μm spatial resolution. All subjects were examined in the supine position in a dark room (illumination <1 lx, measured with an ST-92 luminance meter; Beijing Teachers University Photoelectricity Instrument Factory, Beijing, China). After topical anaesthesia, the globe was placed with an eyecup filled with hydroxyethyl cellulose as a coupling agent. Subjects were instructed to relax and focus on a fixation target about 1 m in front of the eyes to avoid the effect of accommodation. Each eye was examined in the way of radial scan through the centre of the pupil, and images of the 3, 6, 9, 12 o'clock were obtained to represent each quadrant respectively.

All images were measured by one masked observer (Chen SY), using an originally developed semiautomatic measuring software. This measuring software was improved on the basis of UBM PRO 2000 software (Paradigm Medical, Salt Lake City, UT, USA). The following parameters were measured as previously described[7-8] (Figure 1): 1) the ciliary body thickness at the position of 1 mm posterior to the scleral spur (CBT1); 2) the trabecular-ciliary process distance (TCPD) defined as the length of the line extending from the corneal

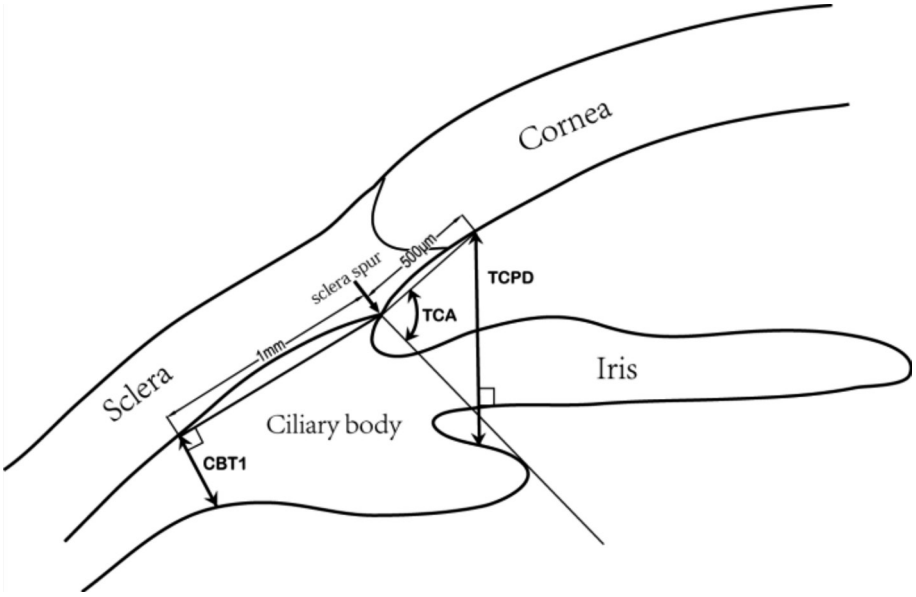

Figure 1 Measurement of the ciliary body parameters The ciliary body thickness (CBT1) was measured at the position of 1 mm posterior to the scleral spur. The trabecular-ciliary process distance (TCPD) was defined as the length of the line extending from the corneal endothelium 500 μm from the scleral spur perpendicularly through the posterior surface of the iris to the ciliary process. The trabecular-ciliary process angle (TCA) was measured with the scleral spur as the apex, and the corneal endothelium and the anterior surface of ciliary process as the arms of the angle.

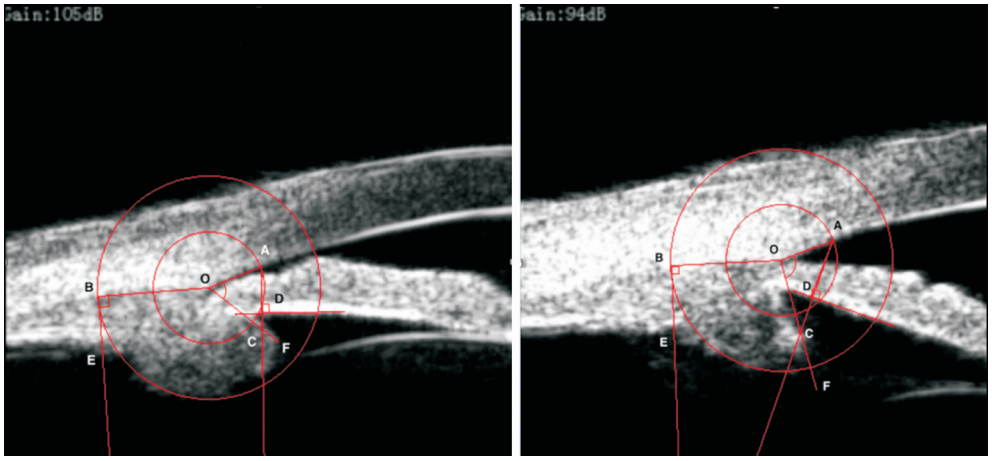

Figure 2 Measurement patterns of ultrasound biomicroscopy images of an eye with angle closure and a normal one There are two circles centered on point O (sclera spurt) with radius of 500 μm and 1 mm. Line AC is perpendicular to the posterior surface of the iris and line BE is perpendicular to the outer surface of the ciliary body (line OB). Line OF is the tangent line of the anterior surface of the ciliary processes. Ciliary body thickness (CBT1) = Distance BE. Trabecular-ciliary process distance (TCPD) = Distance AC. Trabecular-ciliary process angle (TCA) = Angle AOF.

endothelium 500 μm from the scleral spur perpendicularly through the posterior surface of the iris to the ciliary process; 3) the trabecular-ciliary process angle (TCA) measured with the scleral spur as the apex, and the corneal endothelium along with the anterior surface of ciliary process as the two arms of the angle.

The measurement patterns by the software were presented in Figure 2. The semiautomatic measuring procedure was completed as follows: 1) randomly select one image for measurement; 2) mark the sclera spur by the observer and two circles centred on the sclera spur with radius of 500 μm and 1 mm were automatically drawn; 3) mark point A which is the intersection of the smaller circle and the inner surface of the cornea, then draw a line along the posterior surface of the iris and get a perpendicular line to iris through point A automatically, and mark the intersection of the perpendicular line and the anterior surface of the ciliary processes as point C; 4) mark point B as the intersection of the bigger circle and the outer surface of the ciliary body, and get a perpendicular line to line BO automatically, and then mark point E as the intersection of the perpendicular line and inner surface of ciliary body; 5) mark point F to make line OF the tangent line

Table 1 Comparison of demographic data between the two groups before and after PSM

Parameters	Before PSM			After PSM[a]		
	PAC/PACG (*n*=107)	Normal (*n*=108)	*P*	PAC/PACG (*n*=57)	Normal (*n*=57)	*P*
Age, y	66.6±8.4	59.8±10.4	<0.001[b]	63.7±7.8	65.32±7.8	0.282[b]
Gender, M/F	23/84	55/53	<0.001[c]	13/44	18/39	0.293[c]
Eye, R/L	62/45	103/5	<0.001[c]	39/18	55/2	<0.001[c]
SE, D	0.550±1.316	0.337±1.721	0.344[b]	0.628±1.321	0.686±1.697	0.858[b]
IOP, mm Hg	15.87±7.78	14.87±3.26	0.223[b]	15.93±7.17	14.84±2.95	0.297[b]
Diagnosis, *n*						
PAC	82	None		44	None	
PACG	25			13		

[a]PSM: Propensity score matching (1:1 matching with calliper set at 0.02, adjusting for the covariates of age and gender); [b]Independent sample *t*-test, [c]Chi-square test. SE: Spherical equivalent; D: Diopter; IOP: Intraocular pressure; PAC: Primary angle-closure; PACG: Primary angle-closure glaucoma.

of the anterior surface of the ciliary processes; 6) measure distances AC, BE, and angle AOF as TCPD, CBT1 and TCA, and then save the data automatically.

The right eye was chosen to be the studied one unless only the left eye met the eligibility criteria. Images were removed if anterior uveal cysts presented, or the measurement area was beyond the image. Subjects without all four images (at 3, 6, 9, 12 o'clock) were excluded. In order to eliminate the potential influence of the PAS on measurement, we also made a random extraction of one image without PAS from each subject. Intra-observer reproducibility of UBM measurements for such parameters was pretty good as reported in previous studies[7-8,11]. A number of 100 randomly selected images were remeasured by the same masked observer 4wk later after the initial measurement to investigate the test-retest reliability.

Statistical Analysis Description statistics and comparisons for general features of both groups were made by independent *t*-test (for quantitative data) and Chi-square test (for proportion data). If the age and gender were not matched between the PAC/PACG group and normal group, a propensity score matching (PSM, 1:1 matching with calliper set at 0.02, adjusting for the covariates of age and gender) should be performed to minimize the threat of selection bias. Comparisons of all the quantitative parameters between the matched two groups were performed using the independent *t*-test for the data was normally distributed. The comparisons included the general means of the four quadrants, means of each quadrant and the means of images without PAS. Meanwhile, the distributions of non-PAS images among the four quadrants between the matched two groups were compared by Chi-square test. The linear regression analysis was performed to investigate the association between CBT1 and the parameters for the ciliary body position (TCPD, TCA). At last, the intraclass correlation coefficient (ICC, with one-way random effects model) was applied to assess the intra-observer reproducibility.

RESULTS

There were totally 217 PAC/PACG patients enrolled in this study according to the inclusion criteria, and 74 patients were excluded mainly due to acute attack history and other conditions such as combined ocular diseases, intolerable for UBM examination and so on. A number of 120 normal subjects were enrolled in the normal control group. During the UBM images measurement, 36 PAC/PACG patients and 12 normal subjects were excluded for presenting anterior uveal cysts or failed measurement beyond the image area in any quadrant. Then, a total of 215 eyes of 215 subjects (107 patients with PAC/PACG and 108 normal subjects) were eligible for analysis. General information of the subjects was summarized in Table 1. For the age and gender were not matched in the two groups, the PSM adjusting for age and gender was performed. After PSM, 114 eyes of 114 subjects (57 per group) were analysed. The average spherical equivalent and IOP presented no significant differences between the two groups. In the PAC/PACG group, the PAC-to-PACG ratio was approximately 3:1.

After PSM, there were totally 456 UBM images analysed from the 114 eyes. Comparisons of the parameters of ciliary body between the two groups were presented in Table 2. In general means comparison, eyes with PAC/PACG showed significantly thinner CBT1 (PAC/PACG, 0.578±0.097 mm; normal, 0.718±0.112 mm; $P<0.001$), shorter TCPD (0.624±0.124 mm; 0.839±0.167 mm; $P<0.001$) and narrower TCA (63.5°±12.0°; 80.9°±14.3°; $P<0.001$) than the normal eyes. And the results of the quadrant-based comparisons highly agreed with the general means analysis in each quadrant, which suggested that eyes with PAC/PACG had thinner ciliary body thickness and more anteriorly situated ciliary processes.

After excluding images of quadrants with PAS, 110 non-PAS images randomly selected from the matched two groups were measured, and the PAC/PACG group also showed the same features (Table 3). Moreover, the distributions of non-

PAS images among the four quadrants were agreed in the two groups (Chi-square test, P=0.933).

The simple linear regression analysis showed TCPD (R^2=0.537, P<0.001) and TCA (R^2=0.517, P<0.001) had significant correlation with CBT1, both in the whole and in each group (Table 4). The intra-observer reproducibility for the parameters was good in this study. The ICCs for the TCPD, TCA, CBT1 were 0.904, 0.925, 0.847, respectively.

DISCUSSION

In this study, ciliary body thickness was found to be significantly thinner in eyes with PAC/PACG than in normal eyes, after age and gender matched using PSM. Further quadrant-based comparisons and the comparison in images without PAS showed that eyes with PAC/PACG still presented the feature of thinner ciliary body after eliminating potential influence of quadrants and PAS. This study strongly demonstrated thinner ciliary body thickness in eyes with PAC/PACG, supporting the hypothesis that thin ciliary body thickness might be a potential factor for angle closure[7].

This finding is also in agreement with several previous studies. Gohdo *et al*[7] found eyes with narrow angle (Shaffer classification, grade 0 to 2) had thinner ciliary body thickness than normal control eyes. However, Gohdo *et al*'s[7] study only enrolled 36 eyes and was still limited in eyes with narrow but open angle. Li *et al*[10] showed eyes with APAC had thinner ciliary body compared with fellow eyes. Wang *et al*[9,11] also found eyes with APAC and malignant glaucoma presented thinner ciliary body thickness than the matched control eyes. Another study indicated the younger patients with PAC disease presented thinner and more anteriorly rotated ciliary body than the older ones[15]. These studies indicated that thinner ciliary body thickness might also be a predisposing factor for special kinds of angle closure glaucoma such as APAC and malignant glaucoma.

Contrary to the current study, some previous studies found eyes with angle closure had larger ciliary body[16-17]. And it was proved that Valsalva manoeuvre could cause thickening of the ciliary body and induce narrowing of the angle[18]. However, the parameters for ciliary body measured in above studies mainly represented the thickness of anterior part of ciliary body which included ciliary muscle and most stroma, and may be much more variable due to the effect of ciliary processes. While the parameter CBT1 applied in our study measured the relatively posterior ciliary body, mostly the longitudinal fibres. Therefore, we speculated that the reduction of the ciliary body thickness in eyes with angle closure mainly happened on the ciliary muscle. And thickening of the ciliary body during Valsalva manoeuvre was due to venous stasis and rise in episcleral venous pressure, which was not a common state and was avoided during the UBM examination in our study.

Table 2 Comparison of ultrasound biomicroscopy parameters between the two groups after PSM[a]

Parameters	PAC/PACG eyes (n=57)	Normal eyes (n=57)	P^b
CBT1 (mm)			
Mean	0.578±0.097	0.718±0.112	<0.001
Superior	0.557±0.114	0.719±0.176	<0.001
Nasal	0.584±0.134	0.742±0.178	<0.001
Inferior	0.580±0.117	0.690±0.141	<0.001
Temporal	0.591±0.132	0.721±0.139	<0.001
TCPD (mm)			
Mean	0.624±0.124	0.839±0.167	<0.001
Superior	0.580±0.186	0.859± 0.231	<0.001
Nasal	0.651±0.174	0.852±0.200	<0.001
Inferior	0.605±0.157	0.817±0.206	<0.001
Temporal	0.658±0.169	0.827±0.212	<0.001
TCA (degree)			
Mean	63.5±12.0	80.9±14.3	<0.001
Superior	60.8±14.8	85.0±20.8	<0.001
Nasal	67.1±16.8	82.7±17.0	<0.001
Inferior	61.3±14.3	78.2±16.8	<0.001
Temporal	65.4±14.5	81.2±16.6	<0.001

All data are presented as mean±SD. [a]PSM: Propensity score matching (1:1 matching with calliper set at 0.02, adjusting for the covariates of age and gender); [b]Independent sample t-test. PAC: Primary angle closure; PACG: Primary angle-closure glaucoma; CBT1: Ciliary body thickness at the position of 1 mm posterior to the scleral spur; TCPD: Trabecular-ciliary process distance; TCA: Trabecular-ciliary process angle.

Table 3 Comparison of ultrasound biomicroscopy parameters between the two groups after PSM[a] based on non-PAS images

Parameters	PAC/PACG eyes (n=53)	Normal eyes (n=57)	P^b
CBT1	0.545±0.120	0.682±0.130	<0.001
TCPD	0.667±0.178	0.854±0.205	<0.001
TCA	66.1±14.6	82.9±17.7	<0.001

Data are presented as mean±SD. [a]PSM: Propensity score matching (1:1 matching with calliper set at 0.02, adjusting for the covariates of age and gender). [b]Independent sample t-test. PAC: Primary angle closure; PACG: Primary angle-closure glaucoma; CBT1: Ciliary body thickness at the position of 1 mm posterior to the scleral spur; TCPD: Trabecular-ciliary process distance; TCA: Trabecular-ciliary process angle; PAS: Peripheral anterior synechia.

The explanation for thinner ciliary body thickness in eyes with angle closure remains to be clarified. Previous studies showed ciliary body thickness was affected by various factors and might offer explanations. First, as we know old age is one of the risk factors of PACG[19]. Thus thinner ciliary body in eyes with PAC/PACG might be a manifestation of ciliary muscle atrophy related to aging, as showed in histological[20] and

Table 4 Association between ciliary body thickness and ciliary body position after PSM[a]

CBT1	All			PAC/PACG			Normal		
	B	R^2	P^b	B	R^2	P	B	R^2	P
TCPD	1.062	0.537	<0.001	0.813	0.401	<0.001	0.870	0.339	<0.001
TCA	90.2	0.517	<0.001	73.6	0.356	<0.001	75.1	0.347	<0.001

[a]PSM: Propensity score matching (1:1 matching with calliper set at 0.02, adjusting for the covariates of age and gender); [b]Simple linear regression. PAC: Primary angle closure; PACG: Primary angle-closure glaucoma; CBT1: Ciliary body thickness at the position of 1 mm posterior to the scleral spur; TCPD: Trabecular-ciliary process distance; TCA: Trabecular-ciliary process angle; B: Regression coefficient; R^2: Coefficient of determination.

biometric[21-22] studies. However, thinner ciliary body thickness has been found in younger patients with PAC disease[15], which indicates age might not be major factor. Therefore, we applied PSM to diminish the effect of age in this study, and thinner ciliary body was still observed in eyes with PAC/PACG. Second, thinner ciliary body and anteriorly rotated ciliary process were also found in eyes with aniridia combined with ciliary body hypoplasia[23-24]. Therefore, we speculated that such thinner ciliary body in eyes with angle closure might also be related to inherent hypoplasia to some extent. Third, ciliary body thickness was proved to be positively correlated with axial length[25-26], and thinner ciliary body might be explained by shorter axial length in eyes with angle closure. In this study, no significant difference in the spherical equivalent was found between the two groups, even though the data of axial length hadn't been collected. Our previous work showed the difference of CBT1 between the Caucasians and Chinese was independent of axial length[8]. Therefore, shorter axial length might not be the only explanation for thinner ciliary body thickness in eyes with angle closure.

Besides thinner thickness, more anteriorly situated ciliary processes were also found in eyes with PAC/PACG than in normal eyes in the present study, which was widely agreed with previous studies[2,4-5]. And the reduction of the ciliary body thickness was significantly correlated with the anterior situation of the ciliary processes. This correlation has been previously found in normal eyes[8], but not in eyes with angle closure before. As known, anterior situation of ciliary processes was proved to be associated with angle closure, while thinner ciliary body thickness might also be another predisposing factor for angle closure, and might induce angle closure through the same way as anterior situated ciliary processes do. One potential explanation for the effects of thinner ciliary body on angle closure was proposed as follows. Attaching firmly to the scleral spur, the ciliary muscle could prevent ciliary processes from anterior rotation. Thinner ciliary muscle may not be strong enough to attach to the scleral spur and may lead anterior situation of ciliary processes[7], and then induce angle closure through the formation of plateau iris, or cause more anterior and thicker lens with greater lens vault and shallower anterior chamber depth by loosening the zonules[7-9,11].

There are several limitations in this study. First, UBM examinations for all PAC/PACG patients were performed after LPI which differed from that in normal group. Some previous studies suggested widening of the anterior chamber angle (trabecular-iris angle, TIA, angle-opening distance, AOD), deepening of the anterior chamber depth after LPI in eyes with angle closure[27-29], but the effect of LPI on the parameters of ciliary body has been poorly studied with controversial results. In one study TCPD was found to be increased[27], while the other two studies indicated no significant changes of TCPD and CBT after LPI[29-30]. Even if TCPD is increased by LPI, the TCPD of the eyes with PAC/PACG is still shorter than that of normal eyes in this study. Second, the exclusion of the eyes with acute attack history or more than two quadrants of PAS may result in selection bias. Third, the data of axial length was not obtained for further analysis in this study, while the association between CBT1 and ethnicity difference adjusted for axial length was analysed in our previous work[8].

In conclusion, this UBM study demonstrated that eyes with PAC/PACG had thinner ciliary body thickness and more anteriorly situated ciliary processes than normal eyes. And thinner ciliary body thickness was associated with anterior situation of the ciliary processes. Thinning of the ciliary body might be one of the predisposing factors for angle closure. However further experimental study is required to comfirm this as a cause-and-effect relationship between ciliary body thinning and angle closure.

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