EDITOR'S CHOICE

Increased iris thickness and association with primary angle closure glaucoma

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ABSTRACT

Aims To investigate the relationship between quantitative iris parameters and angle closure disease.

Methods Participants with angle closure were recruited prospectively from glaucoma clinics. Anterior segment optical coherence tomography (AS-OCT) was performed under standardised dark conditions. Customised software was used on horizontal AS-OCT scans to measure iris thickness at 750 um (IT750) and 2000 um (IT2000) from the sclera spur, maximal iris thickness (ITM) and cross-sectional area of the iris (I-Area).

Results 167 Angle closure (consisting of 50 primary angle-closure (PAC), 73 primary angle closure glaucoma (PACG) and 44 fellow eyes of acute PAC) and 1153 normal participants were examined. After adjusting for age, sex, pupil size and anterior chamber depth, mean IT750 (0.499 vs 0.451 mm, $p<0.001$), IT2000 (0.543 vs 0.479 mm, $p<0.001$), ITM (0.660 vs 0.602 mm, $p<0.001$) and I-Area (1.645 vs 1.570 mm^2, $p=0.014$) were significantly greater in angle closure (combined groups) versus normal eyes. Multivariate adjusted odd ratios (OR) of each parameter for the angle closure as compared with normal eyes were: IT750 OR1.7 (95% CI 1.1 to 2.7, $p=0.032$); IT2000 OR2.2 (95% CI 1.3 to 3.8, $p=0.006$) and ITM OR2.2 (95% CI 1.3 to 3.6, $p=0.003$), respectively, per 0.1 unit increase.

Conclusions Increased iris thickness is associated with angle closure.

The prevalence of primary angle closure glaucoma (PACG) has been reported to be between 1.0% and 1.4% among Asians 40 years and older.[1 2] PACG is associated with a high rate of blindness and was found to be a leading cause of blindness in East Asian populations.[3 4] Previously reported anatomical risk factors for angle closure include a shallow central anterior chamber depth (ACD), an anterior lens position and short axial length.[5–8] Among these, shallow ACD is regarded as a cardinal risk factor. However, population-based data suggest that only a small proportion of participants with shallow ACD ultimately develop PACG.[9 10]

Laser peripheral iridotomy (LPI), the first-line treatment for PACG, acts by relieving pupil block.[11] Studies have shown that LPI results in a significant increase in the angle width in eyes with narrow angles.[12–19] However, one fifth of eyes have residual angle closure after LPI, and additional therapy is often required to lower intraocular pressure (IOP) especially in eyes with more advanced PACG.[13 18 19] Thus, it is important to investigate the role of other mechanisms in angle closure apart from pupil block.

A recent study from Singapore found that quantitative iris parameters, such as iris curvature, cross-sectional area and thickness, were independently associated with narrow angles in a community-based sample of participants aged 50 years or older.[20] These measurements were obtained using anterior segment optical coherence tomography (AS-OCT). Narrow angles were defined as eyes in which the posterior trabecular meshwork (PTM) was not seen for at least 180° on non-indentation gonioscopy. However, in this previous study, the majority of affected participants had narrow angles only (primary angle closure suspects) without glaucoma, and it is not known if this association is present in patients with more advanced disease such as those with PACG.

In order to further investigate this association in patients with significant angle closure disease, we employed identical study methods and AS-OCT criteria for iris measurements and recruited hospital-based patients categorised into PACG, primary angle closure (PAC) without glaucoma and fellow eyes of participants who had suffered a previous episode of acute angle closure.

METHODS

This was a prospective cross-sectional study. Study participants were consecutively recruited from glaucoma clinics at a tertiary eye hospital in Singapore after obtaining written informed consent. The study was approved by the ethics committee of the Singapore Eye Research Institute and was carried out according to the tenets of the Declaration of Helsinki.

Three subgroups of angle closure and a group of normal participants were examined; the definitions of each subgroup in the study were as follows:[21]

1. Primary angle closure
   These were eyes with narrow angles (defined as eyes in which the PTM was not seen for at least 180° on indentation gonioscopy in the primary position) with peripheral anterior synechaie (PAS) and/or raised IOP (defined as an IOP>21 mmHg) but without glaucomatous optic neuropathy or visual field loss. PAS was defined as abnormal adhesions of the iris to the angle that were present to the level of the anterior trabecular meshwork or higher and were deemed to be present if apposition between the peripheral iris and angle structures could not be broken despite indentation gonioscopy.
2. Primary angle-closure glaucoma
   These were eyes with PAC and glaucomatous optic neuropathy (defined as vertical cup: disc (CD) ratio ≥0.7 and/or CD asymmetry >0.2

and/or focal notching) with compatible visual field loss on static automated perimetry (SITA Standard algorithm with a 24–2 test pattern; Humphrey Visual Field Analyser II, Carl Zeiss Meditec, Dublin, California, USA). This was defined as Glaucoma Hemifield Test outside normal limits with an abnormal pattern standard deviation with p<5% occurring in the normal population and fulfilling the test reliability criteria (fixation losses <20%, false positives <33% and/or false negatives ≤33%).

3. Fellow eyes of acute primary angle closure
   Diagnostic criteria for acute primary angle closure (APAC) were as follows:[22] the presence of at least two of the following symptoms: ocular or periocular pain, nausea or vomiting or both, and an antecedent history of intermittent blurring of vision with haloes; a presenting intraocular pressure of >28 mm Hg on Goldmann applanation tonometry; and the presence of at least three of the following signs: conjunctival injection, corneal epithelial oedema, mid-dilated unreactive pupil and shallow anterior chamber.
4. A control group of normal participants
   A control group of normal participants (defined as IOP ≤21 mm Hg with open angles, healthy optic nerves and normal visual fields, no previous surgery and with no family history of glaucoma). These participants were derived from a cross-sectional study of persons aged 50 years and older who were recruited from a community clinic between December 2005 and July 2006. Details of this population have been described previously.[20 23 24] In brief, participants were participants of a study evaluating new screening instruments for narrow angles were 50 years or older and did not have any ophthalmic complaints, history of glaucoma or previous intraocular surgery.

Patients diagnosed with secondary angle closure (such as neovascular or uveitic glaucoma), patients with corneal abnormalities that would affect AS-OCT imaging, prior history/evidence of APAC in the study eye, laser iridoplasty, history of intraocular surgery and participants on miotic therapy were excluded. All patients with PAC, PACG and fellow eyes of APAC had previously undergone LPI.

Anterior segment OCT imaging

AS-OCT imaging (Visante, Carl Zeiss Meditec) was performed on all participants under standardised dark conditions, that is, with the room lights off (0 lx). Adequate care was ensured to maintain similar imaging environment and room illumination during AS-OCT scan acquisition for both the hospital-based and community-based participants. Scans were centred on the pupil and taken along the horizontal axis (nasal–temporal angles at 0°–180°), using the standard anterior segment single-scan protocol. To obtain the best quality image, the examiner adjusted the saturation and noise and optimised the polarisation for each scan during the examination. As several scans are acquired by the AS-OCT device, the examiner chose the best image, with no motion artefacts, or image artefacts due to the eyelids. For bilateral cases and the control group, only right eyes were imaged.

AS-OCT images were then processed using customised software, the Zhongshan Angle Assessment Program (Guangzhou, China).[25] The only observer input was to determine the location of the two scleral spurs. The algorithm then automatically calculated the following iris parameters: iris thickness (IT750, IT2000 and ITM), iris area (I-Area) and iris curvature (I-Curv) (figure 1). IT750 and IT2000 were defined as the iris thickness measured at 750 and 2000 μm from the scleral spur, respectively. These measurements were performed as follows: A circle with radius of 750 μm was drawn, with the scleral spur used as the centre. The point of intersection at the anterior surface of the iris was identified. The shortest distance from this point to the posterior surface of the iris was calculated as IT750. The same method was used for IT2000. ITM was the highest value of iris thickness along the entire iris. I-Area was calculated as the cumulative cross-sectional area of the full length of the iris. To calculate I-Curv, the software draws a line from the most peripheral to the most central points of iris pigment epithelium, and then a perpendicular line is extended from this line to the iris pigment epithelium at the point of greatest convexity.[26] In addition, ACD, pupil size, angle opening distance (AOD) and angle recess area (ARA) were also measured. AOD was the length of a line drawn from the anterior iris to the corneal endothelium perpendicular to a line drawn along the trabecular meshwork at 500 μm from the scleral spur.[27] ARA was defined as the area bordered by the anterior iris surface, corneal endothelium and a line perpendicular to the corneal endothelium drawn to the iris surface from a point at 750 μm anterior to scleral spur.[28] The average of both temporal and nasal measured values in one meridian was used for the analysis.

Statistical analysis was performed using the statistical package STATA V. 9.2 (StataCorp LP). The difference in iris parameters between clinical confirmed cases of angle closure and normal participants in iris parameters was evaluated using logistic regression models to determine the OR and 95% CI. Multivariate-adjusted ORs were obtained after adjustment for age, sex, pupil size and ACD.

RESULTS

A total of 196 angle closure patients from the hospital-based sample and 1540 normal participants from the community-based sample were studied. Of these, 29 (14.8%) angle closure and 387 (25.1%) normal participants were excluded from analysis due to problems in identifying the scleral spur, leaving 167 angle closure (consisting of 50 PAC, 73 PACG and 44 fellow eyes

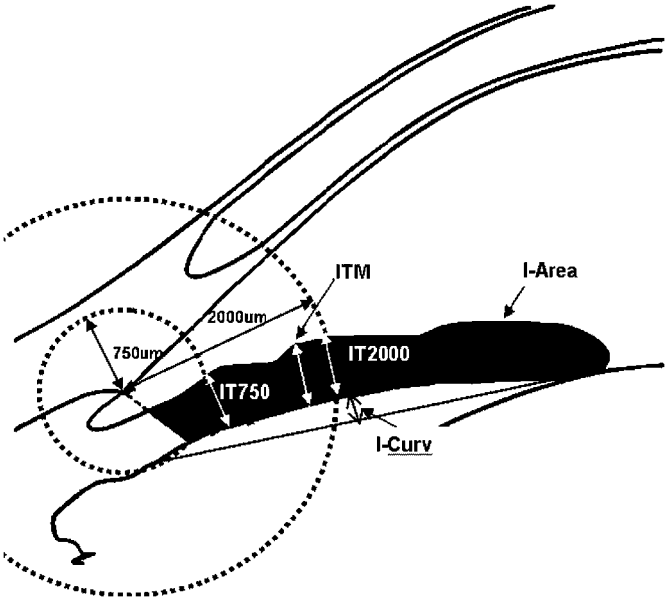

Figure 1 A schematic diagram illustrates the automatic measurement of iris thickness (IT750, IT2000 and ITM), iris area (I-Area) and iris curvature (I-Curv).

of APAC) and 1153 normal participants in the final analysis. The majority of participants (about 90%) in both groups were Chinese (table 1). There were significant differences between the two groups for age (p<0.001), sex (p<0.001), ACD (p<0.001), pupil size (p<0.001), AOD (p<0.001) and ARA (p<0.001). Compared to the control population, the angle closure patients were older, had shallower ACD, narrower angles, smaller pupil size and had more female participants. Visual field mean deviation (MD) in PAC, PACG and fellow eyes of APAC groups were −3.31 (3.73) dB, −9.96 (8.70) dB and −5.29 (5.89) dB, respectively.

After adjusting for age, sex, pupil size and ACD, mean values of IT750 (0.499 vs 0.451 mm, p<0.001), IT2000 (0.543 vs 0.479 mm, p<0.001), ITM (0.660 vs 0.602 mm, p<0.001) and I-Area (1.645 vs 1.570 mm^2, p=0.014) were significantly greater in the angle closure group than in the normal sample, while I-Curv (0.110 vs 0.260 mm, p<0.001) was greater in the normal sample (table 2).

After adjusting for age, sex, pupil size and ACD, the multivariate adjusted ORs of each parameter (95% CI and p value) for the angle closure as compared with normal eyes were: IT750, 1.7 (1.1 to 2.7, p=0.03); IT2000, 2.2 (1.3 to 3.8, p=0.006); ITM,2.2 (1.3 to 3.6, p=0.003); I-Area, 1.1 (1.0 to 1.3, p=0.08) and I-Curv, 0.4 (0.3 to 0.5, p<0.001), respectively, per 0.1 unit increase (table 3).

After adjusting for age, sex, ACD and pupil size, there were significant differences for most of the iris parameters between angle closure subgroups and normals (table 4), except for IT750 for PACG versus normals (p=0.09), I-Area for PACG versus normals (p=0.07) and I-Area for fellow eyes of APAC versus normals (p=0.64).

DISCUSSION

This study confirms our previous report that increased iris thickness is independently associated with angle closure.[20] While the earlier study evaluated narrow angle cases and normals in community-based general health clinics, the present study recruited angle closure cases prospectively from glaucoma clinics at a hospital and included both PAC and PACG cases. The findings from these individuals were similar to those found before, indicating that increased iris thickness is likely to play a role in the development of angle closure and ultimately PACG. After adjusting for age, sex, ACD and pupil size, the iris was thicker in angle closure than in normal eyes.

The results were consistent among all the three iris thickness positions, IT750, IT2000 and ITM, for the combined angle closure group as well as the subgroups of angle closure. It shows that in angle closure eyes, peripheral and maximal iris thicknesses are all larger than those of normal eyes. A thicker peripheral iris is likely to contribute to angle closure as the peripheral iris would be in closer proximity to the angle. This may be especially important in eyes with shallow and crowded anterior chambers. With ageing and increased lens thickness with shallowing of the anterior chamber, it is likely that the increased iris thickness becomes a significant risk factor for angle closure development in such eyes. We speculate that PACG/PAC eyes with thicker peripheral iris may even benefit from treatments to thin the peripheral iris, such as with laser gonioplasty. Interestingly, the multivariate adjusted ORs for IT2000 was higher than that for IT750, suggesting that there may be differences in thickness of more central parts of the iris and possibly even generalised iris thickness. We acknowledge that utilising only three positions to measure iris thickness may not be ideal since they may not be representative of the whole iris, and further studies are warranted.

In contrast, Sihota *et al* found that Indian eyes with acute and chronic PACG had thinner irides when measured using ultrasound biomicroscopy compared to those with sub-acute PACG, primary open angle glaucoma and controls.[29] These measurements were not adjusted for pupil size. We speculate that a previous acute episode can result in ischaemic iris atrophy and a decrease in iris thickness. Hence, we excluded participants with a known history of acute attack and studied the fellow eyes instead. Another possibility is that there are racial differences in iris thickness between Indian and Chinese eyes.

Interestingly, patients with angle closure had a smaller pupil size compared to normal control eyes. In our study, all the patients with angle closure had undergone LPI before AS-OCT imaging; thus, we cannot exclude the possibility that after LPI, the pupil diameter decreased. However, a previous study indicated that there was no statistically significant change in pupil

Table 1 Comparison of angle closure and community normal participants

Measures	Angle closure cases (n=167)	Normal participants (n=1153)	p Value
Age in years, mean (SD)	65.33 (8.33)	62.15 (7.72)	<0.001
Men, number (%)	54 (32.3)	560 (48.7)	<0.001
Race			
Chinese	152 (93.4)	1012 (88.2)	0.36
Other	15 (6.6)	135 (11.8)	
Pupil size, mm, mean (SD)	3.87 (0.79)	4.17 (0.82)	<0.001
ACD, mm, mean (SD)	2.10 (0.33)	3.19 (0.33)	<0.001
AOD, mm, mean (SD)	0.17 (0.10)	0.27 (0.13)	<0.001
ARA, mm^2, mean (SD)	0.14 (0.08)	0.22 (0.09)	<0.001

ACD, anterior chamber depth; AOD, anterior opening distance; ARA, angle recess area.

Table 2 Comparison of iris parameters in angle closure eyes and normal eyes

Iris measures	Mean (SD) in angle closure eyes (n=167)	Mean (SD) in normal eyes (n=1153)	Mean difference (95% CI)*	p Value
IT 750 (mm)	0.499 (0.14)	0.451 (0.10)	0.048 (0.024, 0.072)	<0.001
IT 2000 (mm)	0.543 (0.13)	0.479 (0.10)	0.063 (0.041, 0.085)	<0.001
ITM (mm)	0.660 (0.13)	0.602 (0.10)	0.058 (0.036, 0.080)	<0.001
I-Area (mm^2)	1.645 (0.35)	1.570 (0.27)	0.075 (0.015, 0.135)	0.014
I-Curv (mm)	0.110 (0.27)	0.260 (0.12)	−0.328 (−0.361 to −0.294)	<0.001

*Adjusted for age, sex, pupil size and anterior chamber depth.
IT750, iris thickness measured at 750 μm from the sclera spur; IT2000, iris thickness measured at 2000 μm from the sclera spur; I-Area, iris area; ITM, maximal iris thickness; I-Curv, iris curvature.

Table 3 Relationship of iris parameters and risk of angle closure (combined groups)

Iris measures	Unadjusted OR (95% CI)*	p Value	Multivariate adjusted OR (95% CI)* †	p Value
IT 750	1.3 (1.1, 1.6)	0.001	1.7 (1.1, 2.7)	0.032
IT 2000	1.4 (1.2, 1.7)	<0.001	2.2 (1.3, 3.8)	0.006
ITM	1.5 (1.2, 1.8)	<0.001	2.2 (1.3, 3.6)	0.003
I-Area	1.0 (0.9, 1.1)	0.880	1.1 (1.0, 1.3)	0.083
I-Curv	0.5 (0.4, 0.6)	<0.001	0.4 (0.3, 0.5)	<0.001

*Per 0.1 unit increase.
†Multivariate adjusted for age, sex, pupil size and anterior chamber depth.
IT750, iris thickness measured at 750 μm from the sclera spur; IT2000, iris thickness measured at 2000 μm from the sclera spur; I-Area, iris area; ITM, maximal iris thickness; I-Curv, iris curvature.

Table 4 Comparison of iris parameters between subgroups of angle closure versus normal controls

Measures	PAC (n=50)		PACG (n=73)		Fellow eyes of APAC (n=44)		Normal (n=1153)
	Values	p Value*	Values	p Value*	Values	p Value*	
IT 750, mm, mean (SD)	0.51 (0.25)	<0.001	0.46 (0.11)	0.086	0.49 (0.14)	0.001	0.45 (0.08)
IT 2000, mm, mean (SD)	0.55 (0.24)	<0.001	0.50 (0.11)	0.001	0.52 (0.14)	0.001	0.48 (0.08)
ITM, mm, mean (SD)	0.67 (0.24)	<0.001	0.63 (0.13)	<0.001	0.63 (0.15)	0.010	0.60 (0.07)
I-Area, mm^2, mean (SD)	1.70 (0.47)	0.003	1.56 (0.34)	0.074	1.59 (0.67)	0.640	1.57 (0.23)
I-Curv, mm, mean (SD)	0.10 (0.36)	<0.001	0.11 (0.24)	<0.001	0.11 (0.18)	<0.001	0.26 (0.12)

*Multivariate adjusted for age, sex, pupil size and anterior chamber depth, compared to normal eyes.
ACD, anterior chamber depth; IT750, iris thickness measured at 750 μm from the sclera spur; IT2000, iris thickness measured at 2000 μm from the sclera spur; I-Area, iris area; ITM, maximal iris thickness; I-Curv, iris curvature; PAC, primary angle closure; PACG, primary angle closure glaucoma; APAC, acute primary angle closure

diameter before and after LPI.[12] When we compared the anterior chamber width between the two groups, we found that angle closure patients had a smaller anterior chamber width (11.17+0.42 mm) compared to control eyes (11.80+0.38 mm, p<0.001), indicating that the larger pupil diameter in the dark was not due to the eye being larger. The association between pupil size and angle closure deserves to be further studied. In all the other analyses, we have adjusted for pupil size so as to remove this potential confounding effect.

Iris curvature was significantly smaller in PAC/PACG cases than in normal eyes. This is understandable as all the angle closure patients had undergone LPI before AS-OCT imaging, and it is likely that LPI caused flattening of iris convexity, as found previously in studies using ultrasound biomicroscopy.[12–15] In contrast, our previous study showed that greater iris curvature was associated with angle closure in participants who had not undergone LPI.[20] Although we found that iris area was greater in angle closure eyes compared to normal eyes (in mean values), the multivariate adjusted OR (95% CI) of 1.1 (1.0 to 1.3) was not significant (p=0.08). This may be due to the limited sample size. In our previous study, differences were noted between the lowest and highest quartiles of iris area in an adjusted analysis.[20] Further studies are warranted to confirm if cross-sectional iris area is a risk factor for angle closure.

Important limitations of the current study include the fact that measurements of lens thickness, axial length or refraction were not done. Our sample size was relatively small, and some of the differences found may not have been significant due to the limited power. All angle closure patients had previously undergone LPI, and this may have affected iris measurements. Additional prospective studies are needed to confirm the current findings in participants who have not undergone LPI. Also, some specific questions regarding the use of systemic medicine, which may affect iris structure (such as alpha-1 adrenergic receptor antagonists), were not part of the study protocol. Finally, we performed this study in dark conditions, and we did not evaluate changes in the iris induced by different lighting conditions.

AS-OCT imaging has some limitations. First, although AS-OCT can obtain a full cross-sectional view of the anterior chamber in one image frame, the light source used to obtain AS-OCT images is partially blocked by the sclera and the pigment of the iris resulting in a limited resolution of the ciliary body and the structures posterior to the pigment epithelium. This may also affect precise evaluation of iris morphology. Second, AS-OCT images are associated with a high rate of undetectable scleral spur. In our study, 29 (14.8%) patients from the hospital-based sample and 387 (25.1%) participants from the community-based sample were excluded from analysis due to problems in identifying the scleral spur. Ideally, there is a need to investigate iris parameters in these participants using methods that are not dependent on scleral spur localisation.

In summary, we confirm our previous findings of an association of a thicker iris with angle closure. This was found in a diverse group of angle closure patients recruited from glaucoma clinics and included both PAC and PACG cases. The results suggest that an increased iris thickness may play a role in angle closure pathogenesis.

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Patient consent Obtained.

Ethics approval This study was conducted with the approval of the Singapore Eye Research Institute.

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