Special Focus, Glaucoma

Correlation between choroidal thickness and intraocular pressure control in primary angle-closure glaucoma

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Purpose: To study the correlation between choroidal thickness (CT) and IOP control in primary angle-closure glaucoma (PACG). **Methods:** In total, 61 patients (102 eyes) with PACG underwent subfoveal CT (SFCT) scanning using enhanced depth imaging–optical coherence tomography. The subjects with PACG were further grouped as controlled IOP (≤21 mm Hg on maximal medical therapy) and uncontrolled IOP (>21 mm Hg on maximal medical therapy). The average CT of the PACG eyes was calculated and compared between both groups. A correlation analysis was done between CT and intereye difference in CT with the disease parameters. **Results:** The mean CT was 274.38 ± 42.10 µm in 102 PACG eyes. SFCT was significantly increased in the uncontrolled IOP group as compared with the controlled IOP group. The mean SFCT was 245.57 ± 62.10 µm in the controlled group and 294.46 ± 51.05 µm in the uncontrolled group ($P < 0.01$). Factors associated with a thicker choroid were younger age, high IOP, and higher optic nerve head cupping ($P < 0.001$). Neither the visual field-mean deviation (VF-MD) nor pattern standard deviation (PSD) was found to be associated with overall CT. The intereye asymmetry between CT was significantly associated with poor VF-MD and PSD. **Conclusion:** PACG eyes with thicker choroid may be a risk factor for poor IOP control on medical anti-glaucoma therapy. Thicker choroid as compared to the fellow eye is a poor prognostic sign and these eyes should be monitored closely.

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Primary angle-closure glaucoma (PACG) is a protean disease with a varied clinical presentation. The proportion of those with PACG who become blind (by the World Health Organization definition, <3/60 in better eye) is over 25%, more than twice as high as the estimated blindness proportion for open-angle glaucoma.[1]

Till recently, angle-closure glaucoma was considered primarily as an anatomical disease,[2] but many studies have since established its multifactorial pathomechanism.[3] However, the smaller ocular dimensions, described as anterior nanophthalmos,[4] which includes shallow anterior chamber, a short axial length, thick lens, and hyperopia, explains only about one-third of the variance in the prevalence of PACG.[4,5]

In our clinical observation (unpublished), we have observed that some of the PACG eyes with the same degree of synechiae are controlled with medication whereas there are similar anatomical eyes that continue to progress despite maximal medical therapy. Thus, there may be other dynamic factors likely to contribute to the disease process than just the anatomical variability.[6-8] Recently, there has been a growing evidence of the role of choroid in the pathophysiology of primary angle-closure disease (PACD).[3]

Choroid, which forms the outer 2/3rd of the eye, is a highly vascular tissue contributing more than 90% of the ocular blood flow. In eyes predisposed to angle-closure by their small dimensions, Quigley *et al.* hypothesized that choroidal expansion may push the iris-lens diaphragm forward, initiating or aggravating a closure of the anterior chamber angle.[3] Even a modest expansion of the choroid can dramatically increase the intraocular pressure (IOP), which is not visible clinically.[3] Thus, even with a patent peripheral iridotomy (PI), the angle-closure can continue to progress.

Over the last decade, major advancement has taken place in imaging the choroid.[9,10] Using the enhanced depth imaging (EDI) mode, optical coherence tomography (OCT) has revolutionized the method to study the morphology of the choroid and its role in PACG. Since then, choroidal expansion has been demonstrated in both untreated and treated eyes with acute and chronic PACD.[11-14] However, similar anatomical and physiological factors do not explain the disease asymmetry and difference in IOP control between two eyes of the same individual.

The primary aim of the present study was to find out the correlation between choroidal thickness and IOP control in PACG. Our secondary aim was to find out if an intereye difference in the choroidal thickness contributes to the PACD severity.

Methods

The study was a prospective, observational, cross-sectional design that investigated 102 Indian adult eyes with diagnosed

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PACG. Participants were recruited from the glaucoma services of a tertiary care hospital between May 2016 and September 2016. Both eyes of eligible patients were included for evaluation. Written informed consent was obtained from all study participants, and the study protocol was approved by the institutional review board and performed according to the tenets of the Declaration of Helsinki. Approval from IRB has been obtained Date of approval- 19-02-2016.

A detailed history was taken from each participant, including the duration of anti-glaucoma medications (AGM) usage. A comprehensive ophthalmic assessment was done by a single well-experienced glaucoma specialist and included best-corrected visual acuity, slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy by a Posner 4 mirror goniolens, and a dilated stereoscopic fundus examination with +90 D noncontact lens. An achromatic automated perimetry using the 24-2 Swedish Interactive Threshold Algorithm standard program (Humphrey visual field analyzer) was performed wherever possible, and measurement of axial length and anterior chamber depth was done for all patients using the immersion technique.

The study included diagnosed cases of PACG as per Foster's ISGEO classification.[15] PACG was defined as eyes with narrow angles (eyes in which the posterior trabecular meshwork was not seen for at least 180° on indentation gonioscopy in the primary position) with peripheral anterior synechiae, and/or raised IOP (IOP >21 mm Hg) with glaucomatous optic neuropathy [defined as a vertical cup/disc (C: D) ratio >0.7 and/or C:D asymmetry >0.2 with the same disc size and/or focal notching/thinning] and correlating visual field loss on static automated perimetry. The IOP at first presentation was taken as the baseline.

The exclusion criteria were patients <40 years of age, high myopia or hyperopia [>±6 D (SE) refractive error], any kind of previous ocular surgery, any retinal abnormalities such as diabetic retinopathy, macular degeneration, inflammatory eye diseases, previous retinal laser therapy, and uncontrolled diabetes or hypertension as they can have an effect on choroidal circulation. Media opacities and low-quality images due to cataract and unstable fixation were excluded.

All the eyes enrolled had received a laser peripheral iridotomy (LPI), either before or at the time of diagnosis. The choroidal thickness measurement was done after 2 weeks of the LPI and after instituting the anti-glaucoma treatment. All YAG PIs were done by an experienced glaucoma specialist with minimum of 3–4 shots with 5-mJ energy and hence any inflammation was expected to settle down within 2 weeks. All patients were started on topical prednisolone acetate, QID for 1 week after PI. Patients were divided into two groups: the controlled group when IOP was <21 mm Hg and the uncontrolled group when IOP was ≥21 mm Hg on maximal medical therapy (MMT). Maximal tolerated medication therapy included beta-blockers (timolol maleate), alpha agonists (brimonidine), CAI (dorzolamide/brinzolamide), prostaglandin analogs, and +/− tab acetazolamide/syrup glycerol.

Decision about the timing of surgical intervention in the uncontrolled group was left at the surgeon's discretion.

Choroidal thickness measurement

All measurements were done with the Heidelberg Spectralis (Spectralis software version 5.1.1.0, Eye Explorer Software 1.6.1.0) through dilated pupils by an experienced operator who was masked to the clinical finding of the patients. Choroid imaging was averaged for 100 scans using the device's automatic averaging and eye-tracking features. All images were acquired using the EDI mode with seven radial B-scans centered on the fovea in both horizontal and vertical directions (scan angle: 30° for fovea, scan length: 8 mm; Fig. 1). Image quality was judged based on the signal-to-noise ratio, and only scans with ≤20 dB were considered for analysis. The resultant images were viewed and measured with Heidelberg Eye Explorer software (version 1.5.12.0; Heidelberg Engineering). The choroid was measured from the outer portion of the hyperreflective line corresponding to the retinal pigment epithelium (RPE) to the inner surface of the sclera, which is taken as the best-visualized border between the choroid and the sclera, known as the choroidal–sclera interface (CSI). An average of both horizontal and vertical choroidal thickness scans was taken for analysis. For observer agreement, 25 random choroidal thickness images were again analyzed by manually realigning the CSI by the same observer. The chance corrected and Kappa statistics for intraobserver variability demonstrated satisfactory repeatability (k value, w = +0.59).

Statistical analysis

To be able to detect a difference of 70 microns in choroidal thickness among the study groups, with the standard deviation assumed to be 35 micron (based on a study by Arora *et al.*),[11] with type 1 error of 0.05 and study power of 80%, a sample size of 40 eyes per group is necessary. Statistical analysis was performed using the SPSS software version 18.0. All values are presented as mean ± SD. Gender was assessed with Chi-square test. For comparisons between the two groups, an independent sample *t*-test was used to evaluate differences in the average between the normally distributed data. Univariate linear regression with Pearson's correlation coefficient and multivariate linear regression were used to identify participant characteristics that were associated with CT. Independent variables for the multivariate regression model with a clustering level at the individual level were chosen using the stepwise selection method, with the criterion for inclusion in the model set at $P = 0.10$.

Results

We included 102 eyes of 61 PACG patients: 41 with bilateral PACG and 20 unilateral PACG; 19 eyes were excluded because of poor quality of images. Among the PACG subjects, 42 eyes were in the controlled group and 60 in the uncontrolled group. The baseline demographic characteristics of both groups have been summarized in Table 1. The groups were comparable in terms of age, sex, axial length, visual acuity, refractive error, and anterior chamber depth. The uncontrolled group had significantly higher peripheral anterior synechiae (PAS), with more number of anti-glaucoma medications (AGM). On visual field analysis, mean deviation (MD) was worse in the uncontrolled group, though pattern standard deviation (PSD) did not differ significantly between the groups [Table 1].

On analysis, the mean choroidal thickness was 245.57 ± 62.10 μm in the controlled group and 294.46 ± 51.05 μm in the uncontrolled group ($P < 0.01$) [Table 2]. The uncontrolled arm was 48.89 microns thicker than the controlled group. The intragroup variability in choroidal thickness was not significant, suggesting a homogenous choroidal thickness within both groups.

Univariate regression analysis was conducted to determine parameters related to subfoveal choroidal thickness (SFCT) [Table 2]. Choroidal thickness had a significant positive correlation with both baseline and treated IOP, number of AGM, and C: D ratio. Choroidal thickness

Table 1: Baseline demographic characteristics of the two groups

	Controlled group (*n*=42)	Uncontrolled group (*n*=60)	*P*
Age (yrs)	58±9.18	54.10±9.83	0.30
Sex (m:f)	25:16	33:28	0.494
Spherical equivalent	0.79±1.3	0.67±1.47	0.69
Visual acuity	0.418±8.53	0.57±0.826	0.082
Axial length	22.88±1.029	22.77±1.06	0.45
ACD	2.65±0.29	2.67±0.265	0.47
PAS	111.95±136.2	188±16	0.02
AGM	1.32±1.2	3.2±1.1	0.02
Treated IOP	14.15±3.46	18.36±8.5	0.001
Mean deviation	−7.93±10.3	−20.08±9.63	0.001
PSD	7.66±4.06	9.53±3.5	0.72
Average CT	243.23±60.96	295.230±50.97	0.001

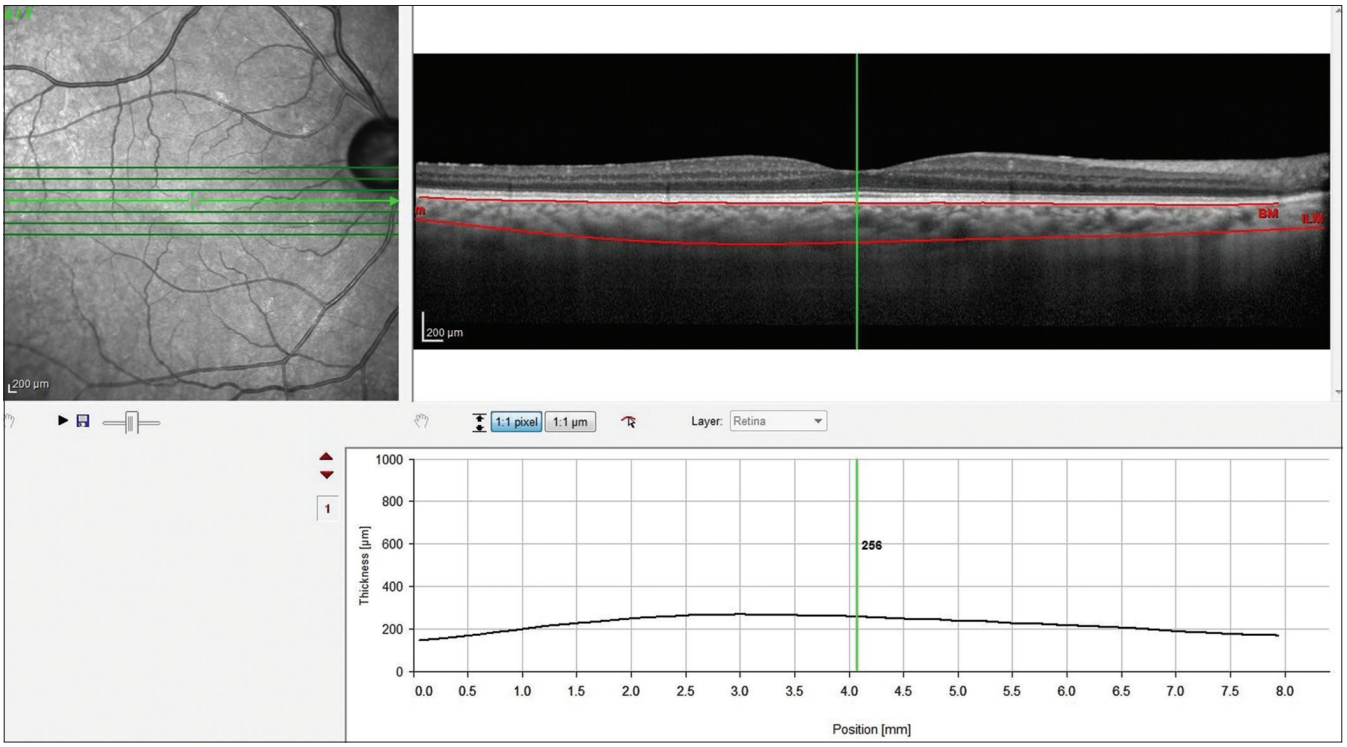

Figure 1: Horizontal scan taken from the fovea. The upper red line shows the hyperreflective layer of the RPE. The lower red line is drawn at the best visualized choroidal sclera interface marked by the dilated Haller's layer

was negatively correlated with age, axial length, and mean deviation.

Multivariate analysis that included all participants identified three variables that were significantly associated with SFCT [Table 3]. Thicker SFCT was related to younger age, higher baseline IOP, and C: D ratio. Even after adjusting for age and baseline measured IOP, increase in ONH cupping was significantly associated with SFCT ($P < 0.001$).

Intereye asymmetry

As glaucoma is an asymmetric disease and the disease course is different in both eyes of the same patient [Fig. 2], we did a univariate analysis between the intereye difference in choroidal thickness and disease parameters of the worse eye. All the severity parameters were found to be higher when the intereye difference in the choroidal thickness was higher [Table 4].

Though no correlation was found between SFCT and disease severity on multivariate analysis when all the PACG eyes were included, for intereye difference in CT and glaucoma severity, higher difference in CT between two eyes was significantly associated with poor mean deviation and higher number of AGM [Table 5].

Discussion

Among eyes with PACD with small dimensions, the reason why some eyes develop an acute type (APAC) while other eyes develop a chronic type (chronic PAC) of angle-closure remains elusive to date. Based on previous studies, PACD is a disease

mediated by small ocular dimensions in addition to abnormal behavior of the uvea. All recent studies have demonstrated that choroidal structure and function may contribute to the pathogenesis of certain angle-closure diseases, but its role in the pathogenesis of disease severity is not clearly elucidated.[11-14] In the present study, we used EDI-OCT to further investigate the correlation between CT and IOP control by comparing the choroid thickness in two groups.

The average choroidal thickness in the normal Indian adult population ranges from 294.8 ± 46.5 μm in the 3rd decade to 249.6 ± 36.0 μm in the 8th decade.[16] In our study, we found the mean SFCT in PACG eyes to be 274.38 micron, which is comparable to the previous studies. In the present study, the uncontrolled group had a greater CT compared with the controlled IOP group (mean difference = 48.9 microns). Greater CT in these eyes may lead to a greater tendency for choroidal expansion and may be related to the poor IOP control in these eyes.

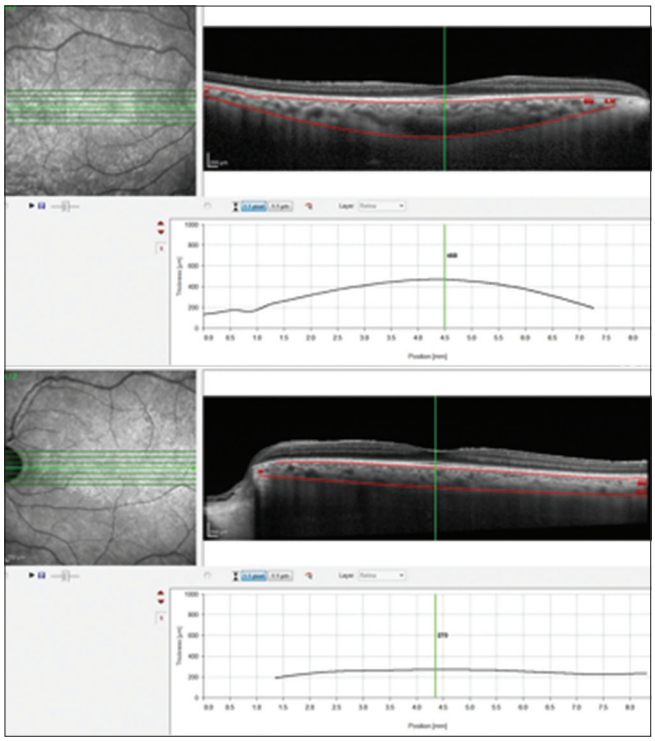

Figure 2: Subfoveal Choroidal thickness of the two eyes of the same patient (right eye followed by the left eye)

Several studies have previously tried to establish a temporal association between choroidal thickness and IOP.[17,18] A study on various subgroups of PACG found that CT in PACG eyes was thinner than in PAC eyes, although the difference was not statistically significant.[13] This may be because of higher IOP in the PACG eyes compared with the other groups, which may reduce choroidal blood volume and cause thinning of the choroid. In our study, eyes with thicker CT had higher treated IOP, were on a higher number of AGMs, and subsequently needed surgical intervention. This may explain the poor IOP control in the uncontrolled group where choroidal expansion may have contributed to the upthrust and worsening the angle-closure despite a patent PI.

Choroid is majorly responsible for the posterior chamber pressure, which is better described as upthrust; it is this pressure that directly affects the optic nerve and is responsible for more damage and rapid progression in PACG than POAG.[1] We plotted an association between CT and disease severity and found a significant correlation with the mean deviation and C: D ratio on univariate analysis, but in multivariate analysis, severity was not associated with thicker SFCT. This can be explained as higher IOP itself is an independent risk factor for advanced field loss. Previously, a lack of relationship was established between CT and the progression of glaucoma based on EDI-OCT measurements as it did not differ between moderate and severe PACG.[12]

SFCT is known to be affected by certain independent factors such as age, axial length, refractive error, diurnal variation, and perfusion pressure.[11] This rightly explains the large range of distribution of CT in both groups. More than CT *per se*, it is the intereye difference in the choroidal thickness which should be considered. A choroidal expansion of 50 microns can increase the IOP significantly.[19] In our study, the intereye difference has a very high positive association with both IOP control and disease severity, even in multivariate analysis. Thus, we recommend that eyes with thicker CT compared to the other eye should be taken as a red flag and be taken as a predictor of poor prognosis.

The results of the present study should be read in view of certain limitations. First, long-term moderate rise in IOP does change the clinical picture and can lead to fallacious

Table 2: Univariate analysis of choroidal thickness in all eyes

n=102	Standardized coeeficient	*P*	Estimates of non-standard coefficients	95% confidence interval for beta (non-standardized)	
	BETA			Lower bound	Upper bound
Age	-5.10	0.01	-5.10	-8.07	-2.12
Axial length	-7.32	0.71	-4.60	-12.94	3.74
Acd	0.55	0.45	0.67	0.46	0.88
Sex	6.40	0.56	-6.65	-25.60	12.30
Se	6.60	0.07	6.60	-0.50	13.70
Baseline IOP	0.45	0.05	-4.21	-6.63	-1.79
Treated IOP	0.25	0.05	-2.79	-7.00	1.43
No of AGM	2.54	0.05	-1.15	-0.71	-1.59
MD	-3.33	0.01	-13.59	-22.41	-4.76
PSD	2.94	0.76	1.46	-0.54	3.46
C: D RATIO	-0.91	0.01	-1.06	-1.70	-0.41

Table 3: Multivariate analysis of choroidal thickness in all eyes

n=102	Standardized coeeficient	*P*	Estimates of non-standard coefficients	95% confidence interval for beta (non-standardized)	
	BETA			Lower bound	Upper bound
Age	-0.34	0.01	-8.34	-12.94	-3.74
Baseline IOP	3.80	0.04	-15.25	-17.40	-13.10
Treated IOP	2.10	0.38	4.00	-3.01	11.01
Mean deviation	-0.80	0.45	-0.55	-2.01	0.91
AGM	0.19	0.12	6.50	-0.16	13.15
C: D	4.20	0.05	7.88	6.64	9.12

Table 4: Univariate analysis of CT in the worse eye of patients with bilateral PACG

n=41	Standardized coeeficient	*P*	Estimates of non-standard coefficients	95% confidence interval for beta (non-standardized)	
	BETA			Lower bound	Upper bound
Age	-12.60	0.01	-12.65	-18.30	-7.00
Axial length	-34.20	0.55	-6.95	-41.10	27.20
Acd	0.64	-2.30	0.88	-2.30	4.06
Sex	2.9.4	0.56	-5.65	-15.60	4.30
Se	6.60	0.07	6.10	-0.50	12.70
Baseline IOP	31.80	0.05	-26.30	-49.20	-3.40
Treated IOP	26.30	0.05	-31.85	-60.20	-3.50
No of AGM	4.39	0.05	-43.85	-76.40	-11.30
MD	-27.90	0.01	-27.90	-35.40	-20.40
PSD	3.94	0.76	1.61	-0.54	3.76
C: D RATIO	16.20	0.01	-16.20	-22.40	-10.00

Table 5: Multivariate analysis of CT in the worse eye of patients with bilateral PACG

n=41	Standardized coeeficient	*P*	Estimates of non-standard coefficients	95% confidence interval for beta (non-standardized)	
	BETA			Lower bound	Upper bound
Age	-11.90	0.01	-11.90	-15.70	-8.10
Baseline IOP	3.80	0.04	-15.25	-17.40	-13.10
Treated IOP	2.10	0.38	-7.01	-3.01	-11.01
Mean deviation	-0.71	0.03	-1.46	-2.01	-0.91
AGM	0.19	0.02	3.32	2.32	4.32
C: D	0.78	0.01	66.00	46.00	86.00

correlation. Second, manually performed choroidal thickness measurements are subject to a bias by the examiner. Automated segmental measurement software is warranted for a more objective evaluation of choroidal thickness. The lens thickness was not assessed, which could be a confounding factor as increased lens vault is a risk factor for angle closure.

Conclusion

In PACG eyes, thicker choroids are associated with higher IOP and more severe disease. It is the intereye asymmetry between choroidal thickness that can be used as a disease severity predictor. CT is an important measurement for every angle closure eye as it can be the third factor involved in the disease pathogenesis other than the angle and the lens. A thickened choroid as compared to the other eye should always raise caution in managing such patients. An early surgical intervention with proper precautions to avoid hypotony is warranted for these eyes as they have poor IOP control even with maximum medical therapy. A prospective study can be planned to determine the rate of progression and CT at baseline and serial visits.

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Conflicts of interest

There are no conflicts of interest.

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