Indian Journal of Clinical and Experimental Ophthalmology 2020;6(4):542–548

Content available at: https://www.ipinnovative.com/open-access-journals

Indian Journal of Clinical and Experimental Ophthalmology

Journal homepage: www.ijceo.org

Original Research Article

Central corneal thickness and intraocular pressure in primary open angle glaucoma suspects in a south Indian population. Is it time for "corneal anthropology"?

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ARTICLE INFO

Article history:
Received 28-04-2020
Accepted 01-05-2020
Available online 22-12-2020

Keywords:
Corneal anthropology
Central corneal thickness
Glaucoma suspects
Intraocular pressure

ABSTRACT

Purpose: To study correlation between central corneal thickness (CCT) and intraocular pressure (IOP) in the primary open angle glaucoma (POAG) suspects and to assess the importance of the local population reference CCT in pachymetry adjusted IOP.
Design: Prospective, cross sectional study.
Materials and Methods: A total of 100 patients aged 40-70 years of age diagnosed as POAG suspects were included. CCT measurements using ultrasound pachymetry and IOP measurement with Goldmann applanation tonometer (GAT) was done. IOP was corrected to the local south-Indian baseline CCT and also to the International CCT and comparison was done.
Results: The study included 100 patients (58 male and 42 female) with mean age of 51.7 ± 6.1 years. The mean CCT was 518.91 ± 24.26 μm, 522.19 ± 21.56 μm among females, males respectively. The mean uncorrected IOP (GAT) was 19.50 mmHg, 20.14 mmHg (right, left sides). Significant, moderate positive correlation between CCT and IOP was observed. The two groups i.e mean IOP corrected for South-Indian CCT (Mean_CX_IOP) versus IOP corrected for CCT international (Mean_CX_INT_IOP) showed significant difference. The mean IOP in Indian CCT corrected group was 19.76 ± 2.81 mmHg and in international CCT group was 21.51 ± 2.83 mmHg. Levene's test indicated significant difference in mean IOP of 2 groups (p=0.000).
Conclusions: CCT is an important parameter in glaucoma management and known to vary in different ethnic groups. Local ethnicity specific CCT should be used in IOP correction with the help of anthropologists.

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1. Introduction

Glaucoma is a major cause of ocular morbidity and irreversible blindness. Globally by this year 2020, around 65.5 million people are expected to be suffering from primary open angle glaucoma (POAG) and black population has the highest POAG prevalence in all age groups except the Hispanics in over 80 years age group.[1] Reliable intraocular pressure (IOP) measurement is important in diagnosing and monitoring progress of POAG. Of various factors central corneal thickness (CCT) has been found to affect IOP measurements by Goldmann applanation tonometer (GAT) significantly. The OHTS found CCT to be a strong predictor of glaucoma and it defined thinner CCT as one of the risk factors for OHT to progress to POAG.[2] This may be due to the under-estimation of IOP in thinner corneas leading to undetected initial glaucomatous changes or also due to other possible underlying biomechanical risk

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https://doi.org/10.18231/j.ijceo.2020.114
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independent of IOP.

In thinner corneas, IOP is recorded falsely low and in thicker corneas it is falsely high. In OHTS, the relative risk of POAG was 1.71 for every 40 μm decrease in CCT. As it is well known that normal-tension glaucoma patients have thinner CCT and POAG suspects have thicker CCT readings, CCT correction of IOP does help to avoid misdiagnosis. CCT is one of the most heritable ocular parameter and varies between various ethnic populations.[3] Recently, many authors have argued against the importance of CCT correction in IOP measurements and POAG management, giving more importance to the corneal biomechanics. However most eye care facilities in developing countries still rely on applanation tonometry for glaucoma management and hence CCT correction of IOP still does hold its importance. Considering the importance of ethnicity in CCT measurement, we tried to compare the mean IOP readings if not corrected for CCT, the mean IOP after adjusting for reference CCT for south-Indian urban population (520 μm)[4] and IOP correction with CCT values according to international consensus i.e 545 μm (according to a meta-analysis & review of 80 studies).[5]

2. Materials and Methods

It was a prospective, non-interventional, comparative study conducted at Dr B.R.Ambedkar medical college & hospital, Bangalore, Karnataka (south-India). The study included 100 patients (200 eyes) from 40 to 70 years age who attended the outpatient department over a period of 1 year, 6 months, clinically diagnosed as primary open angle glaucoma suspects.

The study was approved by the institutional ethics Committee and adhered to the tenets of the declaration of Helsinki. After taking the consent, detailed ocular, systemic & family history was taken. The best spectacle corrected visual acuity (BSCVA) was recorded, slit lamp examination was performed to rule out any corneal/anterior segment pathology including infection and inflammation. On examination POAG suspects were patients with open anterior chamber angles on gonioscopy, with consistently elevated IOP (>21mmHg) associated with normal appearance of the optic disc and retinal nerve fiber layer and with normal visual field test results (Automated Perimetry – Octopus 301 Field Analyser using HFA standard analysis).

Patients with angle closure on gonioscopy, those already on glaucoma treatment, patients who have undergone glaucoma surgery/refractive surgery/cataract surgery and patients with secondary causes for open-angle glaucoma, such as pseudoexfoliation (exfoliation syndrome), pigment dispersion, and traumatic angle recession were excluded.

IOP was measured in both eyes using calibrated Goldmann Applanation Tomometer (GAT) after anaesthetising the eye with topical proparacaine 0.5% and using 2% Fluorescein strips. CCT was measured with ultrasonic pachymeter and average of five measurements was taken as final reading to be used in analysis. We used ultrasound pachymetry for measuring CCT as it has the least inter & intra-observer variability as compared to optical pachymetry. The Pachymetry adjusted (Corrected IOP) was computed using the following formula:

2.1. Corrected IOP = applanation IOP + [5 mm Hg (mean normal – measured CCT μm) / 70 μm]

On the basis of above findings, the study population was divided into three groups which were Group A: Low CCT (<510 μm), Group B: CCT (510-530 μm) and Group C: Patients With High CCT (>530 μm). In the three groups, IOP (GAT) was compared with the South-Indian reference CCT corrected IOP (Mean_CX_IOP) and the international reference CCT corrected IOP (Mean_ CX_INT_IOP).

2.2. Statistical analysis

Statistical Package for Social Sciences [SPSS] for Windows, Version 24.0. NY: IBM Corp., was used to perform statistical analyses. Student Paired t test was used to compare the mean values of different study parameters between the right & left sides. Pearson correlation test was used to assess the relationship between CCT & IOP on the right & left sides. Independent student t test was used to compare the mean IOP for CCT. The level of significance [p-Value] was set at $p<0.05$. The relationship between each IOP (GAT) measurement (IOP, CX_IOP, CX_INT_IOP) and central corneal thickness (CCT) was investigated using linear regression. Levene's test was used to compare Mean_CX_IOP and Mean_ CX_INT_IOP.

3. Results

A total of 200 eyes were evaluated in patients diagnosed as POAG suspects. The patient population consisted of 42 females & 58 males with average age of 51.7 $\pm$ 6.1 years. The mean CCT among females was 518.91 $\pm$ 24.26 μm and among males was 522.19 $\pm$ 21.56 μm. The difference in mean CCT of Right side (520.05 $\pm$ 24.21 μm) & Left side (521.57 $\pm$22.22 μm) was not statistically significant (p=0.17).

The mean Uncorrected IOP (GAT) on right side was 19.50 mmHg & on the left side was 20.14 mmHg & was statistically significant (p=0.003). The Corrected IOP (Pachymetry adjusted IOP) was 19.50 mmHg, 20.03 mmHg on the right, left sides respectively the difference being statistically significant (p=0.01) (Table 1).

Pearson correlation demonstrates a significant & moderate positive correlation between the CCT & IOP for the right side (r=0.39) and the left side (r=0.36) statistically significant (*P*=0.001) (Table 2). Linear regression analysis revealed moderate positive correlation between the mean

CCT and mean uncorrected IOP (p<0.001, r=0.39**) (Figure 1). Figure 2 shows low negative correlation (-0.16) between Mean_CX_IOP and Mean_CCT and Figure 3 shows low negative correlation (-0.15) between Mean_CX_INT_IOP and Mean_CCT values.

Corneal thickness varies in different ethnic populations as discussed later. International standard is different from mean thickness in our population. We took 520 μm as the mean south-Indian baseline CCT and 545 μm as international baseline CCT to be used in the correction of IOP.[5] Table 3 shows the mean IOP when corrected for south-Indian baseline CCT increased from 18.5 mmHg to 20.278 mmHg in the <510 μm group and decreased from 21.3448 mmHg to 19.397 mmHg in <530 μm group. For international baseline CCT correction of IOP, the >530 μm group showed a slight decrease in IOP but the <510 & 510-530 μm groups showed significant increase in IOP (by 3.51 mmHg & 1.76 mmHg respectively).

The mean IOP corrected for south-Indian CCT (Mean_CX_IOP) versus IOP corrected for CCT international (Mean_CX_INT_IOP) showed significant difference. The IOP in Mean_CX_IOP group (n=100) was 19.76 $\pm$ 2.81 mmHg and in the Mean_CX_INT_IOP group (n=100) was 21.51 $\pm$ 2.83 mmHg (Table 4). Levene's test indicated that the variances are equal across the two groups (Sig 0.948). The p=0.00 (< 0.05) indicates that there is significant difference in the mean IOP of the two groups (Table 5).

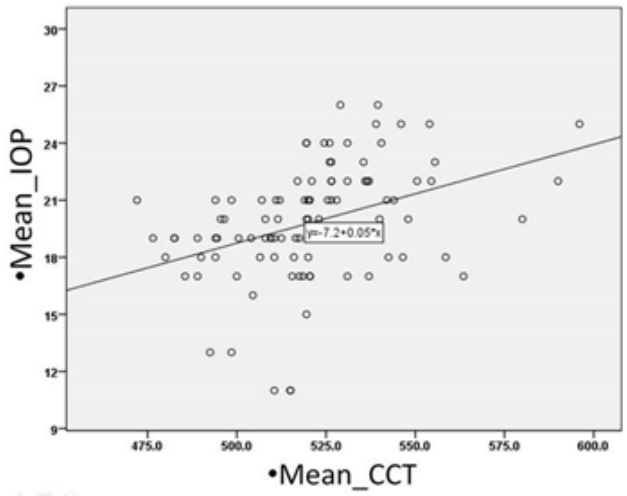

Fig. 1: Scattergram of central corneal thickness (CCT) versus uncorrected intraocular pressure (IOP) [CCT (μm), IOP (mmHg)]

4. Discussion

POAG suspect is diagnosed by the presence of one of the following conditions: consistently high IOP, a suspicious-appearing optic nerve head or abnormal visual fields.[6] IOP has been consistently recognized as the only modifiable risk factor for open angle glaucoma.[7] Accurate IOP measurements are of paramount importance in glaucoma diagnosis and management.

In our study, a total of 200 eyes were evaluated in patients diagnosed as POAG suspects. In The Ocular Hypertension Treatment Study, older age was one of the baseline factors that predicted the development of POAG in both univariate and multivariate analyses along with other factors.[2] In the Aravinda Comprehensive Eye survey, a study from our region, the median age of those with glaucoma was 60.0 years (mean 60.8 years).[8] In our study population, the mean age was 51.7 $\pm$ 6.1 years which was lower than previous studies probably signals the need of thorough glaucoma screening/evaluation. In our study, 58% of study population

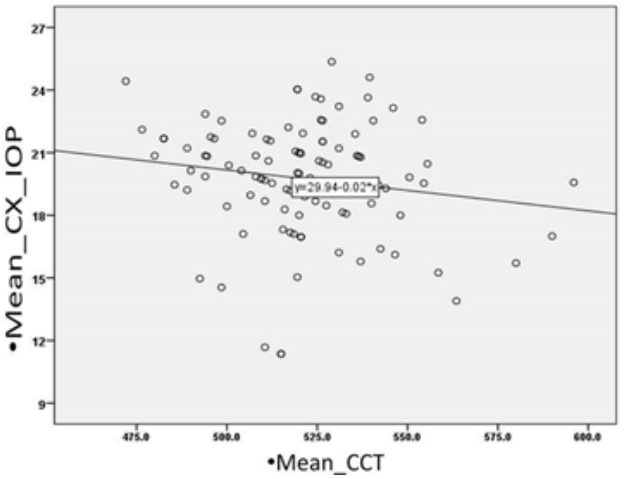

Fig. 2: Scattergram of central corneal thickness (CCT) versus south-Indian reference CCT corrected IOP (Mean_CX_IOP) [CCT (μm), IOP (mmHg)]

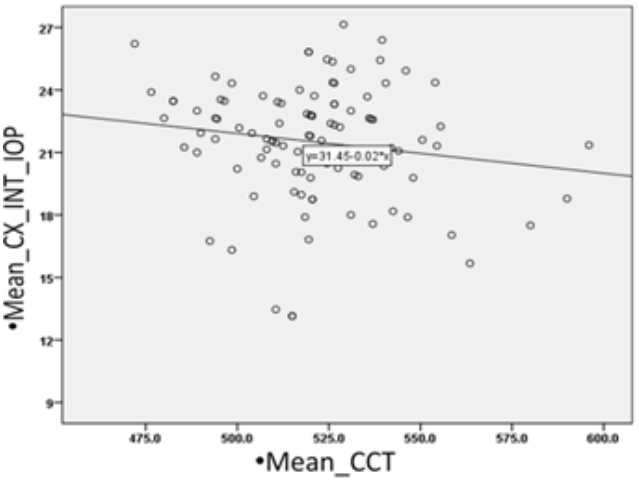

Fig. 3: Scattergram of central corneal thickness (CCT) versus International reference CCT corrected intraocular pressure (Mean_CX_INT_IOP) [CCT (μm), IOP (mmHg)].

Table 1: Comparison of mean values of different study parameters between right, left sides

Comparison of mean values of different study parameters between the right & left sides using Student Paired t test							
Variables	**Sides**		**Mean**	**SD**	**Mean Diff**	**t**	**P-Value**
CCT	Right	100	520.05	24.41	-1.52	-1.370	0.17
	Left	100	521.57	22.22			
IOP	Right	100	19.50	3.32	-0.64	-3.096	0.003*
	Left	100	20.14	3.05			

*Statistically Significant

Table 2: Pearson correlation test to assess the relationship between CCT and IOP on right, left sides

Pearson correlation test to assess the relationship between CCT & IOP on the right & left side				
Sides	**Variable**	**Values**	**CCT**	**IOP**
Right	CCT	r	1	0.39
		-Value		<0.001*
Left	CCT	r	1	0.36
		-Value		<0.001*

*Statistically Significant

Table 3: The relationship between different CCT and IOP

	Mean_IOP (mmHg)			**Mean_CX_IOP**			**Mean_CX_INT_IOP**		
CCT	**Mean**	**Standard Deviation**	**Count**	**Mean**	**Standard Deviation**	**Count**	**Mean**	**Standard Deviation**	**Count**
<=510 μm	18.5000	2.0092	28	20.2782	2.1458	28	22.0120	2.1508	28
510-530 μm	19.6512	3.3444	43	19.6697	3.1649	43	21.4122	3.1934	43
>530 μm	21.3448	2.7029	29	19.3972	2.8438	29	21.1829	2.8446	29

Table 4: Group Statistics: Mean IOP(mmHg) in South-Indian corrected IOP

International reference CCT corrected IOP					
	Group		Mean	Std. Deviation	Std. Error Mean
CX	CX_IOP	100	19.761050	2.8125728	.2812573
	CX_INT_IOP	100	21.513650	2.8254840	.2825484

Table 5: Independent samples test

		Levene's Test for Equality of Variances		**t-test for Equality of Means**						
		F	Sig.	t	df	p-value	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
CX	Equal variances assumed	.004	.948	-4.396	198	.000	-1.7526000	.3986719	-2.5387879	-.9664121
	Equal variances not assumed			-4.396	197.996	.000	-1.7526000	.3986719	-2.5387880	-.9664120

was male and 42% were females. Some studies show males to be more likely to have POAG[8,9] and the others show a higher prevalence in females.[10]

Clinically, GAT is considered the gold standard for IOP measurement.[11] Ehlers in 1975 demonstrated GAT to be accurate with a CCT of 520 um.[12] Various previous studies have reported significant under and overestimation of IOP (GAT) in thinner/ thicker corneas respectively.[13–15] In the OHTS & EGPS[16] studies, the average CCT in OHT group was around 570 μm and CCT<555 μm was associated with increased risk of developing POAG. Kniestedt et al,[17] in their study showed patients with thin CCT are more likely to be found at an advanced stage of glaucoma and concluded that under-estimation of IOP by GAT could be one important causative factor.

So the measurement of CCT may help in correct interpretation of IOP readings apart from other biomechanical factors. As per Ehlers & Hansen, GAT

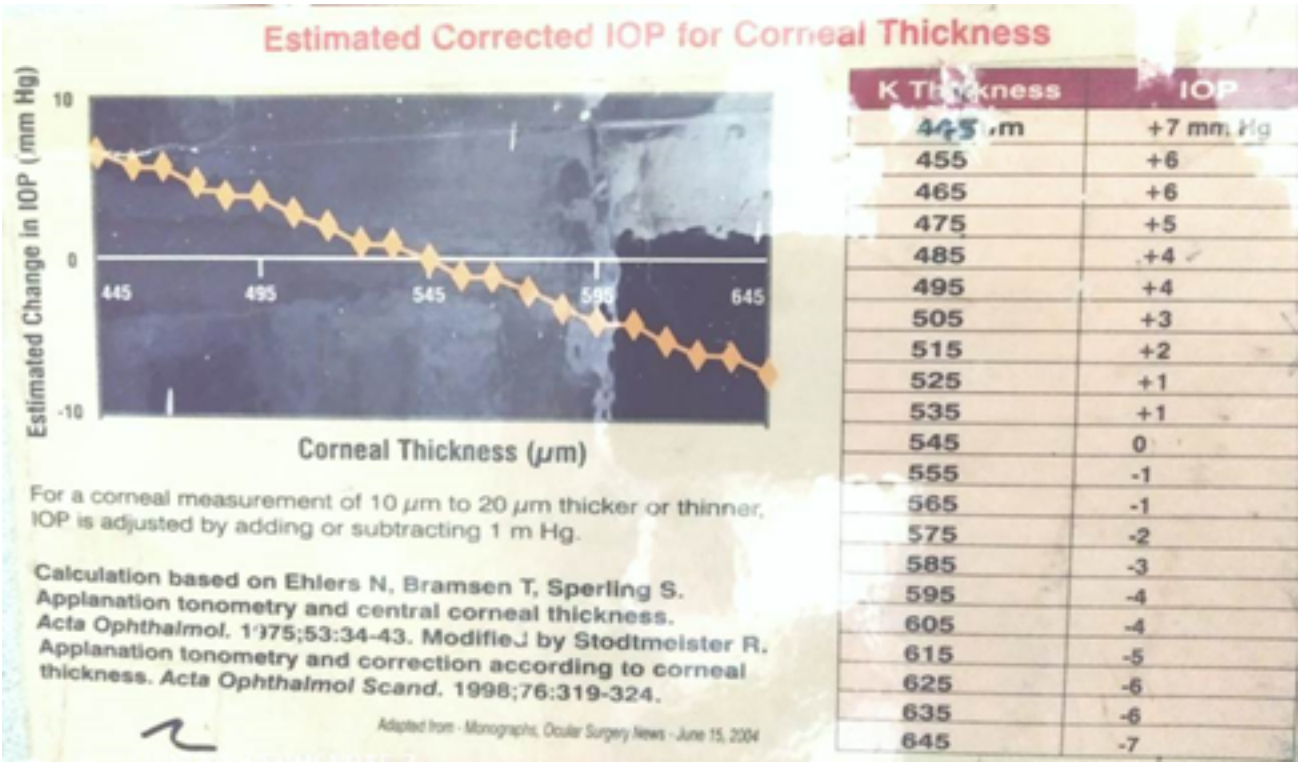

Fig. 4: Correction table in a Indian glaucoma clinic for correcting IOP based on CCT (International)

under/overestimated IOP by 5 mmHg for every 70 um of corneal thickness.[18] The following correction formula for CCT adjusted IOP readings was used.

Corrected IOP = Applanation IOP + [5 mmHg (mean normal CT - normal CCT) / 70um].

CCT is one of the most heritable traits and is known to vary with the ethnic identity.[3] It is a known fact that white race (Caucasians) have thicker corneas than African American dark races.[19] Further, mixed races in South Africa had mean CCT greater than Africans but thinner than Caucasians.[20] In a retrospective study, African Americans had the thinnest CCT (521 μm) followed by the Japanese group (531.7 μm) which was thinner as compared to the other Asian groups like Chinese, Filipinos and also the Caucasians.[21] From the Asia pacific region, there have been many studies which tell us the significant ethnic variation in the CCT. In the Singapore Epidemiology of Eye Diseases study the mean CCT was significantly higher in the Chinese group (552.3 $\pm$ 33.4 μm) as compared to both Malays and Indian group (around 540 μm).[22] In the Yunnan Minority Eye study from China, the Han ethnicity had significantly thin mean CCT (529.6 $\pm$ 32.7 μm) as compared to the Bai and Yi ethnicities (536 $\pm$ 34.2 μm, 532.1 $\pm$ 32.1 μm respectively).[23] The Hong-Kong Chinese have a higher mean CCT (555.11 $\pm$ 35.30 μm).[24] whereas the Burmese mongoloids have significantly thinner corneas (mean CCT= 521.9 $\pm$ 33.3 μm).[25]

From northern Indian Subcontinent, Godar et al. from Nepal reported differences between various ethnicities. Brahmins for instance had cornea thicker by around 10 μm (Indo-European ethnic group) as compared to Gurung ethnicity (mongoloid sub group).[26] As anthropology studies suggest, India has various diverse ethnic groups.[27] There have been very few studies done on Indian population groups with regards to the corneal thickness. A study done in rural central India (the central India eye & medical study) found a mean central corneal thickness to be 514 μm.[28] In south Indian population (The Chennai Glaucoma study) the mean CCT for the urban population was 520.7 $\pm$ 33.4 μm and in the rural group with glaucoma was significantly lower (505.9 $\pm$ 31.1 μm).[4] In our study population mean CCT was 522.19 μm for males & 518.91 μm in females which is closer to the urban group of the Chennai Glaucoma study from the same region as even ours was a urban study. There is still limited data on baseline CCT of different ethnic groups as most authors fail to identify the ethnicity and often resort to the "self-reported" strategy.

4.1. Correlation Between CCT and IOP

Pearson correlation demonstrates a significant and moderate positive correlation between the CCT and IOP for the right (r = 0.39) and the left side (r = 0.36) statistically significant at (p=0.001). This is in accordance with previous studies.[13,29]

The importance of taking corneal thickness into account in normal tension glaucoma, ocular hypertension has already been emphasized by many authors.[13,14,30]

Table 3 shows the mean IOP when corrected for south-Indian reference CCT increased from 18.5 mmHg to 20.28 mmHg in the <510 μm group and decreased from 21.34 mmHg to 19.39 mmHg in <530 μm group. On correcting the IOP for international reference CCT, the >530 μm group showed a slight decrease in IOP but the <510 & 510-530 μm groups showed significant increase in IOP (by 3.51 mmHg & 1.76 mmHg respectively).

4.2. Correlation between south-Indian CCT corrected IOP & international CCT corrected IOP

There is a difference of 25 microns of difference between south-Indian (520 μm) or International (545 μm) reference CCT. So, when adjusting IOP according to south-Indian versus International reference CCTs, there is a significant difference of mean corrected IOP (19.76 $\pm$ 2.81 mmHg in south-Indian versus 21.51 $\pm$ 2.83 mmHg in International) (Table 4). Also, the Levene's test indicates that there is significant difference in the mean IOP of the two groups; p=0.00 (< 0.05) (Table 5).

As seen in Figure 4, majority of clinicians even in India use the algorithm which was based on the adjustment of IOP based on reference CCT values in the international consensus.[31] This causes inaccurate over-correction of IOP in normal tension glaucoma or ocular hypertension patients with leading to their aggressive treatment as compared to IOP adjustment according to Indian reference CCT. This tells us the importance of local ethnicity based reference CCT for IOP adjustment as also concluded in the Yazd Eye study from Iran.[32]

Independent association of CCT with the progression of glaucomatous visual field changes has also been explained. Lesk et al. demonstrated increased compliance (movement) of lamina cribrosa in eyes with thinner CCT due to IOP fluctuation possibly leading to RGC axon damage and glaucomatous changes.[33] In recent studies, the role of CCT adjusted IOP in glaucoma management has been argued against giving more importance to the corneal biomechanics.[34] It is a relatively new concept in glaucoma management and needs more studies to validate the advantage.[35] Nevertheless, even corneal biomechanics has been shown to be affected by the ethnic identity which gives us more hope for "corneal anthropology" in future.[36–38] Ocular response analyser (ORA) may not be available in majority of eye care facilities in developing countries, and hence the use of pachy-corrected-IOP is more practical and may still hold it's importance in the coming times as well.[39,40]

Our study had few limitations. It was a hospital based study, a population based study with more numbers may be needed to substantiate the results. Even though GAT is considered the reference standard, still readings may suffer from the inherent variability and inaccuracy during measurement. Difference in CCT, among various races may contribute to the racial difference of prevalence of open angle glaucoma. We did not specify the exact ethnicity of the patients as it would be difficult in a urban location and hence the role of anthropologists in our field. But the mean CCT is still supposed to be more closer to the native population than an international meta-analysis. More data on ethnicity-specific CCT apart from other cornea parameters with increased role of anthropologists is needed and hence we introduce a new term "corneal anthropology".

5. Conclusion

The pachymetry adjusted IOP values is still a valuable tool in glaucoma management and helps in more accurate IOP readings and avoiding misdiagnosis in open angle glaucoma. In our experience CCT of local Indian population, rather than international thickness should be used to obtain pachy adjusted IOP values.

6. Source of Funding

None.

7. Conflict of Interest

The authors declares that there is no conflict of interest regarding the publication of this article.

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Cite this article: Sharma R, Nagaraja K S, Sujatha R, Prashant C N, Sharma S, Sharma A. Central corneal thickness and intraocular pressure in primary open angle glaucoma suspects in a south Indian population. Is it time for "corneal anthropology"?. *Indian J Clin Exp Ophthalmol* 2020;6(4):542-548.