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Article Central Corneal Thickness In Individuals With And Without Pseudo Exfoliation Syndrome – A Prospective Study

Dr.Priyadharsini[1], Dr.S.Padmanaban[2],Dr.P.Sathya Priya[3] ,Dr. Prayagi Kandoth[4]
Department of Ophthalmology, Coimbatore Medical College Hospital, Coimbatore, Tamil Nadu, India
Corresponding Auther: Dr.Priyadharsini

Abstract :Aim: *To compare the central corneal thickness inindividuals with and without pseudo exfoliation syndrome.* ***Methods:*** *This was a hospital based cross sectional, comparative study. 50 individuals with unilateral or bilateral pseudo exfoliation syndrome (study group) and individuals without pseudo exfoliation syndrome (control group), both without any corneal pathology and glaucoma were included in the study. The CCT was measured by an ultrasonic pachymeter. The IOP was measured by Goldmannapplanation tonometer and was adjusted for the CCT values.****Results:*** *There was no significant correlation between CCT and age. The mean CCT was 0.515± 0.07 mm in the control group and 0.501 mm ± 0.07 mm in study group (P value=0.001). The mean IOP was almost similar in both groups. However, the IOP after CCT adjustment was significantly higher in the study group than the control group.* ***Conclusion:*** *The mean CCT was significantly lower in the individuals with pseudoexfoliation than in individuals without pseudo exfoliation. There was no significant difference in the CCT between the eye with PEXF and its fellow eye in unilateral pseudo exfoliation syndrome.*
Key words:*Central corneal thickness, pseudo exfoliation syndrome.*

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I. Introduction

Glaucoma is one of the leading causes of irreversible blindness throughout the world. WHO statistics indicate that glaucoma is the second leading cause of blindness globally after cataracts.[1]It has been estimated that about 12 million people are affected by glaucoma in India and the majority of themare undiagnosed.[2]In Southern India, the prevalence of glaucoma has been estimated to be around 2.6% & 90% of these cases have never been diagnosed before, compared to 50% previously undiagnosed in European countries. [1]Pseudo exfoliation is the most common cause of secondary open angle glaucomaPseudoexfoliation syndrome was first described by Lindberg in 1917. .The prevalence of pseudo exfoliation differs in different population. The prevalence of PEXF in South India is around 6%[10].The prevalence was found to increase with age and was greater in males.

Goldmann's applanation tonometry (GAT) is the gold standard technique of measuring the IOP.[3] IOP measurements by GAT are affected by various factors among which Central Corneal Thickness is considered the most important. [4,5] CCT which was initially presumed to be fixed and constant, is now found to be affected by various factors such as race, age, etc.[6]The variations in the CCT significantly influence the IOP measurements by GAT. GAT tends to overestimate the IOP in thicker corneas and underestimates the IOP in thinner corneas.[8]The CCT was found to be thicker in patients with ocular hypertension and thinner in cases of normal tension glaucoma, primary open angle glaucoma and pseudo exfoliation glaucoma.Hence, though the measurement of CCT, is mandatory in all cases of glaucoma, special emphasis must be given in those who are at an increased risk of developing glaucoma such as Pseudo exfoliation syndrome to facilitate early diagnosis and an appropriate management by determining the exact target pressure to be attained and to ensure the adequacy of treatment.

Pseudo exfoliation in the anterior chamber angle is evident in gonioscopy by the presence of patchy pigment deposition on the trabecular meshwork, more marked in inferior quadrant and the presence of Sampolesi's line.The presence of pseudo exfoliation affects every part of the anterior segment and results in the following complications:corneal endothelial decompensation, decreased corneal sensitivity, thinning of central cornea, poor dilatation of the pupil, cataract ,melanin dispersion.

Central corneal thickness is one of the very important parameters significantly affecting the IOP measurements by GAT .Few studies have demonstrated that the CCT measurement has a significant influence on glaucoma management and has led to significant modification in the treatment options.

II. Materials & Methods

This is a hospital based, cross sectional study undertaken at the Department of Ophthalmology, Coimbatore Medical College and Hospital, Coimbatore.
The study period was about 12 months extending from November 2012 to October 2013.

Patients attending the Ophthalmology Out Patient Department & those admitted in the wardwere selected on the basis of the following criteria:

Inclusion Criteria: Adult patients of age 50 years & above with or without cataract.

Exclusion Criteria: Patients with the following conditions in any one or both the eyes were excluded from the study by detailed history taking and clinical examination.

1.any cornealpathology ,2.uveitis,3.ocular trauma,4.history of glaucoma,5**.**intraocular pressure> 21 mmhg **,**6**.**field defects and fundus changes suggestive of glaucoma,7.history of contact lens wear**,** 8.history of previous intra ocular surgeries,9.diabetes mellitus.

All the patients aged 50 years and above were selected on the basis of the above criteria and writtenconsent was obtainedA slit lamp examination was done with undilated pupil in all patients to rule out corneal pathologies like keratitis, corneal opacity, edema, scar, dystrophy, ectasia, and degeneration. Uveitis, conjunctival blebs, aphakia, pseudophakiawere also ruled out. All were examined for the presence or absence of pseudo exfoliation. Pseudo exfoliation was diagnosed by the presence of white flakes or fibrillo granular material on the pupillary margin.A slit lamp examination was done again with a dilated pupil to detect presence of PEXF on anterior lens capsule. The presence or absence of cataract and if present the grading of cataract was noted.

Blood samples were taken to measure the random blood sugar and urine analysis was done. Only those individuals with RBS values less than 140 mg% and nil urine sugar were included in the study.

Visual acuity, visual field examination,gonioscopyand refractionwere done for all patients.A detailed fundus examination was done to rule glaucomatous changes. The IOP was measured using GAT. CCT was measured using ultrasonic pachymetry (PAC SCAN 300 P). The details of the patient along with the IOP of both eyes were fed into the pachymeter. After instillation of 0.5% proparacaine, the patients were made to sit upright looking straight ahead. The tip of the hand held pachymeter probe was placed perpendicularly on the cornea and centered over the undilated pupil. An average of five consecutive readings will be recorded. The predesigned software incorporated in the pachymeter auto adjusted the IOP according to the CCT and gave the true IOP along with the mean CCT value.

The patients with CCT adjusted IOP > 21 mm Hg, those with fields and fundus changes suggestive of glaucoma were excluded from the study. The patients who fulfilled all the above criteria were designated as study subjects based on the presence of PEXF on the pupillary margin and/or the anterior lens capsule. Those without PEXF were designated as controls. A total of 100 subjects without PEXF and 50 subjects with PEXF were included in the study. Their IOP and CCT values were tabulated and analysed for statistical significance.The data analysis and interpretation was done using SPSS 16 version. The mean, standard deviation, standard error of mean,degree of freedom, 2-tailed significance and 95 % confidence interval were calculated. Independent t test, one way analysis of variance (ANOVA) and Pearson's correlation were used for analysis of the results.

III. Results

Among the 100 subjects of the control group, 40% were males and 60 % were females. In the 50 subjects of the PEXF group, 54% were males and 46 % were females. The below table shows that within the PEXF group, the number of males were higher (54 %) than females(46%).

Table 01. Gender distribution in both the groups

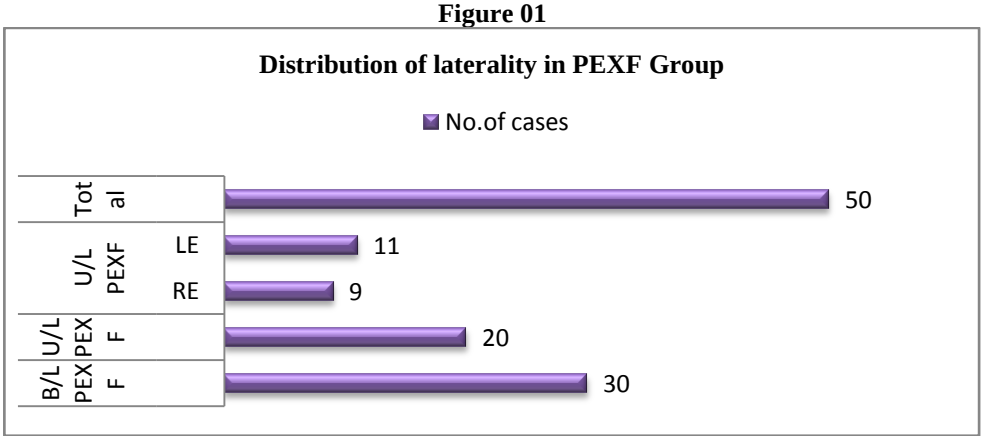
Gender	ControlGroup		PEXF Group		Total	
	No. of patients	%	No. o patients	%	No. of patient	%
Male	40	40	27	54	67	44.7
Female	60	60	23	46	83	55.3
Total	100	100	50	100	150	100

The below table and figure 01 shows that in the PEXF group, 60% had bilateral PEXF and 40 % had unilateral PEXF (18 % in RE alone and 22% in LE alone)

Table 02: Distribution of Laterality of PEXF in the study group

	Bilateral PEXF	Unilateral PEXF	Unilateral PEXF		Total
			RE	LE	
No.of case	30	20	9	11	50
Percentag	60%	40%	18%	22%	100%

Figure 01



The below table shows that the mean CCT is almost same in all age groupsexcept those aged 80 years and above in whom there is marked decrease in CCT compared to the other three groups. This difference was statistically insignificant (p value=0.352)

Table 03: Correlation between age & CCT in study & control groups

Age group (years)	No. of Patients	Mean CCT (in mm)
50-60	40	0.513
60-70	66	0.513
70-80	39	0.512
>80	5	0.476
Total	150	0.511

The below table shows that the mean CCT in the control group without PEXF is 0.517± 0.07 mm in BE. This also shows that there is no difference in the CCT value between both eyes (RE=0.476 LE=0.316).

Table 04. Mean CCT in control group without PEXF

No of patients		Mean CCT (in mm)	Std deviation	Std error mean
100	RE	0.517	.03448	.00345
	LE	0.517	.03371	.00337

The below table shows that the mean CCT in the PEXF group is 0.501± 0.07 mm in RE and 0.500 ± 0.06 mm in LE. This also shows that there is no difference in the CCT value between both eye

Table 05. Mean CCT in PEXF group

No. of patients		No. of eyes	Mean CCT (in mm)	Std Deviation	Std error of mean
50	RE	39	0.501	0.03504	0.00496
	LE	41	0.500	0.03240	0.00458

The below table shows there was no variations in the CCT of both the eyes of bilateral PEXF group.

Table 06. Comparison of CCT between both eyes in B/L PEXF group

No of patients		Mean CCT (in mm)	Std. Deviation	Std. Error Mean
30	RE	0.503	.03664	.00669
	LE	0.503	.03437	.00628

Among the 20 cases with unilateral PEXF, the eye with PEXF had a thinner CCT (0.494 ± 0.06 mm) when compared with the fellow eye without PEXF (0.499 ± 0.07 mm). However, this difference was statistically insignificant (P value =0.644) (Table 07)

Table 07. Comparison of CCT between both eyes in U/L PEXF group

No of patients		Mean CCT (in mm)	Std. Deviation	Std. Error Mean
20	Eye with PEXF	0.494	.028644	.006405
	Eye without PEXF	0.499	.033630	.007520

The below table shows that the CCT is significantly thinner in both the eyes of PEXF groupthan both the eyes in the control group without PEXF(P value RE= 0.008 LE = 0.003)

Table 08. Mean CCT in control group without PEXF and the study group

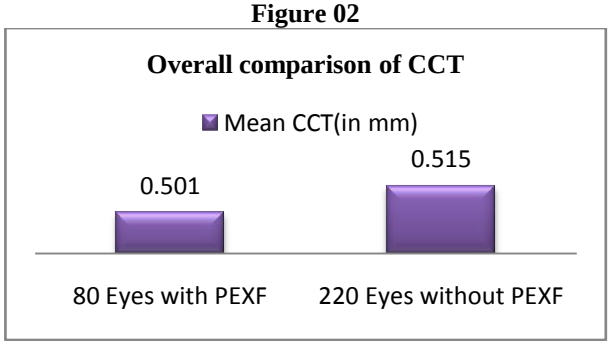
GROUP	No. of patients	MEAN CCT(in mm)	
		RE	LE
Without PEXF	100	0.517	0.517
With PEXF	50	0.501	0.499

The below table and figure 02Comparison of 80 eyes with PEXF in the PEXF group with the 220 eyes without PEXF (200 eyes in the control group and 20 eyes in the unilateral PEXF group) also showed a significant thinning in the eyes with PEXF (P value=0.001)

Table 09. Overall comparison of CCT in eyes with and without PEXF

Group	No. of patients	Mean CCT(in mm)	Std. Deviation	Std. Error Mean
Eyes with PEXF	80	0.501	.033767	.003775
Eyes without PEXF	220	0.515	.034318	.002314

Figure 02

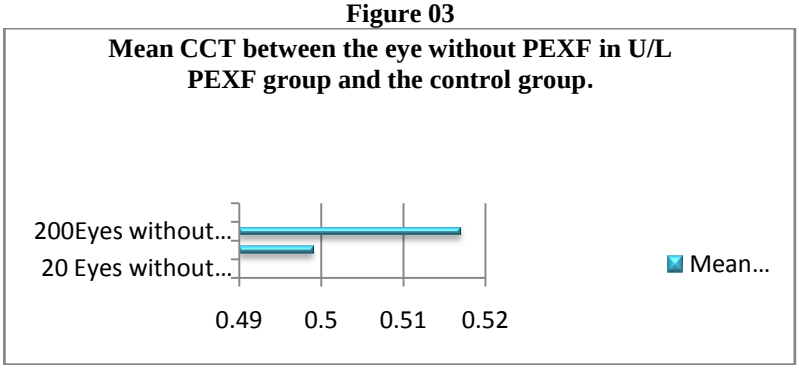


The below table and figure 03 shows that the mean CCT is significantly thinner in the unilateral PEXF group even in the eyes without PEXF when compared with the normal group. (P value= 0.021)

Table 10: Comparison of mean CCT between the eye without PEXF in unilateral PEXF group and the control group.

Group	No. of patients	Mean CCT (in mm)	Std. Deviation	Std. Error Mean
Eyes without PEXF in U/L PEXF group	20	0.499	.033630	.007520
Eyes without PEXF in Control group	200	0.517	.034010	.002405

Figure 03

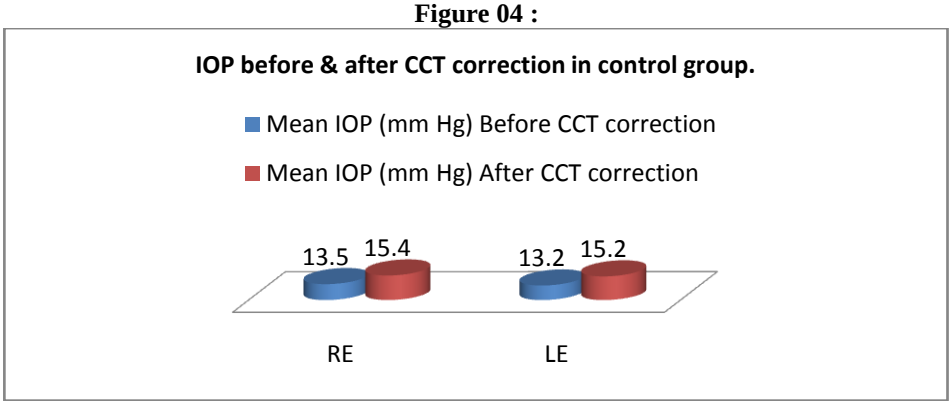


The below tableand figure 04 shows that there is an increase in the IOP of about 1.9 mm Hg in RE and 2 mm Hg in LE after CCT correction in the control group. This increase in IOP was statistically significant. (P value=0.000)

Table 11. Comparison of IOP before& after CCT correction in control group.

	Mean IOP (mm Hg)	
	Before CCT correction	**After CCT correction**
RE	13.5	15.4
LE	13.2	15.2

Figure 04 :

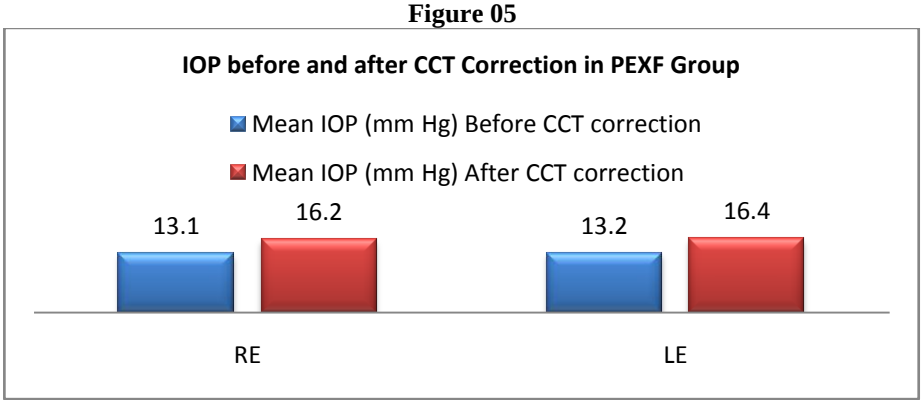


The below table and figure 05 shows that there is an increase in the IOP of about 3.1mm Hg in RE and 3.2 mm Hg in LE. after CCT correction in both eyes of the PEXF group. This increase in IOP was statistically significant. (P value=0.000)

Table 12. Comparison of IOP before& after CCT correction in PEXF group.

	Mean IOP (mm Hg)	
	Before CCT correction	**After CCT correction**
RE	13.1	16.2
LE	13.2	16.4

Figure 05

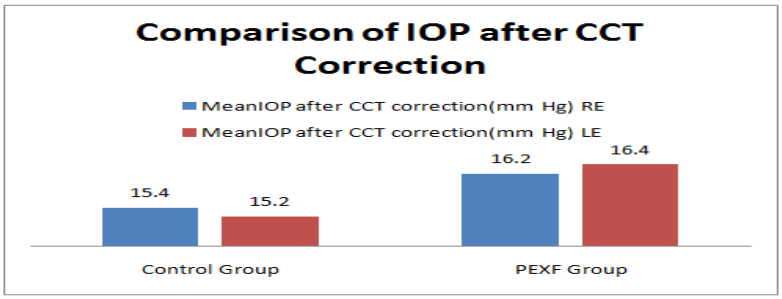


The below table and figure 06 shows that the IOP after CCT correction is higher in the PEXF group than the control group. The difference was statistically significant between the two groups.(P value=0.049)

Table 13. Comparison of IOP after CCT correction between the control group and study group.

	MeanIOP after CCT correction(mm Hg)	
	RE	LE
Control Group	15.4	15.2
PEXF Group	16.2	16.4

Figure 06



IV. Discussion

Pseudo exfoliation is the most common cause of secondary open angle glaucoma. The Blue Mountains eye study showed that the incidence of glaucoma in eyes with PEXF is 9 times higher (14.2%) than the eyes without PEXF(1.7%).The eyes with PEXF have a higher risk, which is independent of other risk factors including IOP.They are associated with a thinner CCT,which leads to an underestimation of IOP and thereby a delayed diagnosis.Thinner CCT itself serves as another independent risk factor for development of glaucoma.All these factors coupled together place the individuals with PEXF at a very high risk of advanced glaucomatous damage than primary open angle glaucoma.The CCT was evaluated using an ultrasonic pachymeter. A minimum of 3 measurements are required for an accurate measurement. The reliability of measurements is fairly good in this study as five measurements were taken for each eye.

In the control group without PEXF, the mean CCT was 0.517 mm. There was no significant difference between both the eyes. The mean CCT in PEXF group was 0.501 mm in RE and 0.500 mm in LE. Most of the studies have reported that CCT decreases with age. [7]But, in this study, a significant relationship was not established between age and CCT. The mean CCT was almost similar in all the groups. There was a decrease in CCT in those aged more than 80 years when compared with those aged less than 80 years. However, 60% of them had PEXF and hence the thinning was due to age or the presence of PEXF could not be ascertained. The difference was statistically insignificant too.(P value=0.352) Certain other studies have also shown that there is no significant relation between CCT and age.

The comparison of CCT between the control group and the PEXF group showed that the CCT was thinner in the PEXF group than the control group without PEXF. This difference proved to be statistically significant too. (P value RE= 0.008 LE =0.003). To support this, an overall comparison of the CCT was made between the 80 eyes with PEXF and the 220 eyes without PEXF (200 eyes of the control group and the 20 fellow eyes without PEXF in the unilateral group). This also showed a significant thinning of the central cornea in those 80 eyes with PEXF than the 220 eyes without PEXF. (P value=0.001)

This shows that the presence of pseudo exfoliation is strongly associated with a significant thinning of the cornea. This is attributed to the apoptosis of the keratocytes of the anterior corneal stroma. [11]Similar results were established by the studies by Hepsen et al , Mohammed Ali Zare et al.and various others.[9]A still stronger evidence of the association of PEXF with a thinner CCT can be established if the CCT is compared between the eye with PEXF and the fellow eye without PEXF in the same individual. This may eliminate the age and gender related bias.So far only very few studies have been reported analyzing the difference in CCT between both eyes with unilateral PEXF.

In this study, the difference in CCT between the eye with PEXF and the fellow eye without PEXF was analyzed in 20 patients with unilateral PEXF. The eyes with PEXF had a slightly thinner CCT (0.494 mm) than the eyes without PEXF(0.499mm). However, the difference was statistically insignificant (p value= 0.644).

Based on this alone, it cannot be concluded that the association of PEXF with thinner CCT in this study is only a coincidence. The fellow eyes of eyes with PEXF, though did not show evidence of PEXF by slit lamp examination, might have had occult deposition of PEXF material in the ocular structures which are too difficult to be detected by clinical examination.

This is supported by the discovery of the fact by Zheng et al. [11]who studied the ultra structural changes in eyes with unilateral PEXF by in vivo confocal microscopic examination and compared them with the fellow eyes without PEXF and also the control population without PEXF. They observed that the corneal endothelial cell density was significantly reduced in both the eyes with PEXF and their fellow eye without any clinical signs of PEXF. They also reported that there was evidence of deposition of hypereflective material suggestive of PEXF on the corneal endothelium, not only in the eyes with PEXF but also in 51.9% of the fellow eyes without PEXF. The subbasal nerve plexus also showed similar changes in the fellow eyes of the eyes with PEXF. Therefore, they suggested that the fellow eyes could have been in a preclinical stage of PEXF.

Based on the above studies, it can be explained that the 20 subjects with unilateral pseudo exfoliation in this study might have had asymmetric involvement and this could be the reason for the absence of any significant difference in the CCT between the two eyes.A comparison of CCT was made between the 20 eyes without PEXF in the unilateral PEXF group and the 200 eyes without PEXF in control group. The 20 fellow eyes of eyes with unilateral pseudo exfoliation, though did not have any evidence of PEXF on slit lamp examination, had a significantly thinner CCT when compared with the 200 eyes of the control group. This difference, proved to be statistically significant too (P value=0.021). This too supports the fact that those 20 eyes might have been at a pre clinical stage of PEXF. However, more sophisticated techniques like in vivo con focal microscopic examination are required to support this fact.

The mean IOP before adjusting for CCT value was almost similar in both eyes of the control group. Following adjustment of the IOP values for the CCT values, there was an increase in theIOP of about 1.95 mm Hg in both the eyes. The increase in IOP was found to be statistically significant too. (P value= 0.000)

In the PEXF group, the average IOP before adjustment for CCT was 13.1mm Hg and 13.2 mm Hg in the right and left eyes respectively. The difference in IOP between both eyes was very minimal. Following correction of IOP for CCT, there was an increase of about 3.1 mm Hg in the IOP of both the eyes. The increase in IOP was statistically significant too. (P value=0.000)

Both the control and the PEXF groups had an almost similar IOP before CCT correction. There was an increase in the IOP following adjustment for CCT in both the groups. This shows that the IOP has been underestimated by GAT in both the control group and the PEXF group. The underestimation in the IOP in the PEXF group can be explained by the presence of pseudo exfoliation and the associated significant corneal thinning which causes an underestimation.

However, there was an underestimation of IOP in the control group too which suggests that the CCT is thinner than the average in the control group too. The reason for thinner corneas in the study group, without any obvious local or systemic causes, is unclear. A possible explanation for this could be offered by the fact that the CCT differs in different population. Various studies have proven the same.[6] Moreover, the definition of mean CCT has also been controversial. There is a wide variation within a given population. While few studies show that the average CCT in Indian population is 0.520 mm, there are few other studies which show that it is about 0.545 mm. A prefixed mean CCT, therefore, cannot be applied for every population.

In this study, the pachymetry device used has been calibrated in such a way that the mean CCT is 0.545 mm. Any value below this, will underestimate the IOP and any value above this overestimates the IOP. The control group had a mean CCT of only 0.517 mm. This explains why there is an underestimation of IOP in them.However, this mean CCT observed in the study population may not be applicable to the entire community.

The significant increase in IOP following adjustment of CCT in the control groups observed in the study emphasizes the measurement of CCT in all the patients and adjusting the IOP measurements by GAT accordingly for an accurate measurement of the true IOP. Although the mean CCT was slightly thinner in the control group, it was considered as the baseline CCT for the entire study population and the CCT in PEXF group was compared with it. The PEXF group demonstrated a still more thinning than the control group which was statistically significant too. This shows that there is a strong association of PEXF with thinner CCT.

Though the IOP before adjustment for CCT was similar in both the study and control groups and there was a significant increase in the IOP following adjustment for CCT in both the groups, the increase in IOP was dissimilar (1.9 mm Hg in the control group versus 3.1 mm Hg in the PEXF group). The CCT adjusted IOP was higher in the PEXF group than the control group and the difference was statistically significant too. (P value=0.049) The higher IOP in the PEXF group after CCT adjustment has been already explained by the fact that the CCT is significantly thinner in them and therefore they had a more pronounced underestimation of the IOP than the control group.

Most of the studies have shown that the IOP is higher in eyes with PEXF than the eyes without PEXF. A similar result was also obtained in this study.This study has demonstrated that the CCT is thinner than average in both the study group and the control group and therefore emphasizes the measurement of CCT in all individuals for an accurate measurement of IOP. The PEXF group exhibited a still more significant thinning of the central cornea and a significantly higher risk of underestimation of IOP compared with the control group. The individuals with pseudo exfoliation are at greater risk of developing glaucoma than those without PEXF. A thinner CCT itself may act as an additional risk factor for development of glaucoma and along with this, there is an underestimation of IOP resulting in a delay in diagnosis. All these factors lead to advanced disease at the time of presentation.

Measurement of CCT, therefore, is necessary in all cases of pseudo exfoliation for prediction of the risk of development and progression of glaucoma, for early diagnosis and to ensure adequacy of treatment.

V. Conclusion

The CCT was significantly thinner in the eyes with pseudo exfoliation than the eyes without pseudo exfoliation. In individuals with bilateral pseudo exfoliation, there was no significant difference between both eyes.

However, in the individuals with unilateral pseudo exfoliation, a slightly lower CCT was observed in the eye with pseudo exfoliation compared to the fellow eye without pseudo exfoliation. This difference, however, was statistically insignificant.. There was no significant relation between age and central corneal thickness.

Moreover, both the eyes in individuals with unilateral pseudo exfoliation, irrespective of the presence or absence of pseudo exfoliation exhibited a statistically significant thinning when compared with the individuals without pseudo exfoliation. This suggests that the fellow eyes of eyes with might have been at a pre-clinical stage which can be demonstrated by ultrastructural studies like electron microscopy and in vivo confocal microscopy.

There was an underestimation of IOP by GAT in both the groups. However, the underestimation of IOP was more pronounced in the individuals with pseudo exfoliation. Pseudo exfoliation itself is a major risk factor for the development of glaucoma. Being associated with thinner corneas which serve as another independent risk factor for the development and progression of glaucoma, the individuals with pseudo exfoliation are at still greater risk of developing glaucoma. The underestimation of the intra ocular pressure in these individuals further worsens the prognosis due to a delay in diagnosis and inadequate IOP control.

The measurement of CCT is therefore mandatory in both the eyes of all the individuals with pseudo exfoliation syndrome to predict the risk of development of glaucoma, to facilitate early diagnosis and ensure adequacy of treatment.

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