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Does the Central Corneal Thickness (CCT) retain its predictive value as a risk factor in Primary Open Angle Glaucoma patients with Diabetes Mellitus?

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Abstract

Background: Central Corneal thickness (CCT) is thicker in diabetic patients. This may cause the CCT to lose predictive power as a risk factor for primary open angle glaucoma (POAG) in patients with diabetes. **Objective:** To evaluate if CCT of POAG patients with diabetes retains its predictive value as a risk factor. **Methods:** A cross sectional analysis of sequential group of patients with POAG with and without diabetes were evaluated HbA1C in diabetic patients and CCT in both groups was measured and the severity of POAG was evaluated using visual field changes and optic disc changes. The correlation was evaluated using confidence interval and liner regression estimator analysis. **Results:** Five hundred and eighty-seven patients with POAG were evaluated. The mean CCT for the group combined was 540.4±34.9 µm. Three hundred and thirty-seven patients had no history of diabetes and had mean CCT of 531.1±19.6µmTwo hundred and fifty of them had diabetes with mean corneal thickness of 549±20.2µm. CCT retained its predictive value as a risk factor for severity in POAG patient without diabetes ($p<0.05$). CCT however was a less sensitive for evaluating risk/severity in POAG patients with diabetes ($p>0.05$). **Conclusions:** CCT values may not retain its predictive value of severityof POAG in patients with diabetes. Hence, CCT alone may not be a reliable marker and mislead treating physicians

Key Words: POAG, CCT, Diabetes, Severity of POAG, CCT and Diabetes

INTRODUCTION

Central corneal thickness(CCT) is one of the strongest independent markers of primary open-angle glaucoma(POAG) development.Ocular Hypertension Treatment Study (OHTS)[1] and the European Glaucoma Prevention Study (EGPS)[2] both have evaluated and established this association. Both the studies have concluded that irrespective of the age or other associated risk factors, people with thinner corneas are more likely to develop POAG. The risk of developing POAG doubled for every 40 µm decrease in CCT from the overall mean of 573.3 µm in the OHTS and EGPS pooled sample.[3]

One of the most important risk factors for primary open angle glaucoma is an elevated intraocular pressure measured by Goldmann Applanation tonometry (GAT) and is influenced by the individual's CCT. GAT assumes a standard CCT of 520 µm for all corneas.[4] Hence, if the cornea is any thicker or thinner ,the IOP needed to be adjusted to avoid over or underestimation.[5]

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The normal range in most studies was between 427–620 µm. Though most studies have quoted comparable central corneal thickness in primary open angle glaucoma and normal individuals.[6–8], some studies have found that central corneal thickness in primary open angle glaucoma patients is significantly lesser than in the normal population. This has made CCT an individual risk factor for development of POAG,hence denoting that patients with thinner corneas h as of greater chances of developing POAG and in some instrances having greater severity[9–12]

Diabetes is now being studied as a risk factor for development and progression in of POAG.[13–16] From various studies, the CCT in the diabetic patient has also been reported to be thicker than non-diabetic patient.[17,18] This had been thought to be mainly due to deposition of glycosaminoglycan or endothelial pump dysfunction.[18, 19] This could mean that the CCT in patients who have POAG and diabetes could be misleading and CCT may not retain its value as a risk factor and a prognostic predictor.

The aim of this study was to evaluate if CCT still remains a reliable indicator of severity or risk factor in POAG patients in diabetes when compared with those without diabetes.

In this study, we compare the CCT among the patients of POAG with and without diabetes mellitus to evaluate if it retains its predictability on severity of POAG.

MATERIALS AND METHODS

Study Population

This study is a cross-sectional review of patients evaluated and treated at tertiary eye center. Five hundred and eighty-seven patients diagnosed with primary open angle glaucoma were evaluated . Since this was an exploratory analysis, no sample size calculation was needed.

Patients with PACG or any history of intraocular surgery (e.g. vitreoretinal procedures, glaucoma filtration surgeries), with secondary open-angle-closure glaucoma, inflammatory glaucoma, acute congestive glaucoma, high myopia, and optic disc abnormalities were excluded from the study. The research was approved by the ethics committee and the institutional review board of Birat eye hospital,Biratnagar, Nepal and has adhered to the tenets of the declaration of Helsinki.

Study Measurement

For every eligible patient, clinical evaluation was conducted were recorded in a database. Information collected includes the subject's age, sex, refraction, intraocular pressure (IOP) (Haag-Streit, Koeniz, Switzerland) and central corneal thickness (Ocuscan Pachymeter, Alcon, USA). Furthermore, the medical, ocular, surgical, and medication histories of the subjects were obtained from patient files and recorded. Patients with POAG were divided into two groups – nondiabetic and diabetic. Criteria for including a patient as a diabetic was defined as having nonfasting glucose levels 200 mg/dl (11.1 mmol/l) or confirmed cases usually via correspondence from general practitioners, optometrist, or previous treating ophthalmologists and using diabetic medications.Random blood sugar and HbA1C were evaluated at the time of eye examination in diabetic patients.Severity on the basis of cup-disc ratio (CDR) – meaning optic nerve head with larger cups denoting more severe form of POAG, neuro-retinal rim changes and Humphrey Visual FieldAnalysis Score (ZEISS Humphrey 750 Field Analyzer) using Parrish-Anderson andSpeath FieldDamage likelihood score staging system[21].

Statistical Analysis

Statistical analysis was performed using SPSS (version 20, SPSS Inc., Chicago.Mean, standard deviation, Linear regression models, confidence interval and estimation analyzers were used to assess the severity of POAG and correlate with CCT measurements in non-diabetic and diabetic patients.

RESULTS

Five hundred and eighty-seven patients with POAG were evaluated.

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Three hundred and thirty-seven patients had no history of diabetes and two hundred and fifty of them had diabetes.

We analyzed these groups differently to evaluate the thickness of CCT and severity of glaucoma based on visual field findings and optic nerve head- Cup to disc ratios.

The mean CCT for the group combined was 540.4±34.9 µm.

CCT AS A RISK FACTOR FOR SEVERITY OF POAG IN NON-DIABETIC PATIENTS.

The mean CCT among the patients without diabetes was 531.1±19.6µm. Our study showed that the patients with thinner corneas had more severe form of visual field defects. Patient with mild severity had mean CCT of 539.16µm (95% CI: 532.09, 546.24, P<0.05), moderate visual field changes had mean CCT of 537.16µm (95% CI: 528.57,545.75, P<0.05),) ,severe visual field changes had mean CCT of 529.18µm (95% CI 506.55, 551.81,P<0.05),) end-stage visual field changes had mean CCT of 519.30µm (95% CI 506.08, 532.53, P<0.05),) (Table1).

Table 1: Severity of VFD in patients with POAG without Diabetes mellitus and analysis with the CCT.

HUMPHREY VISUAL FIELD ANALYSIS			STATISTICS	STD.ERROR
MILD	Mean		539.16	3.562
	95% Confidence Interval for Mean	Lower Bound	532.09	
		Upper Bound	546.24	
MODERATE	Mean		537.16	4.285
	95% Confidence Interval for Mean	Lower Bound	528.57	
		Upper Bound	545.75	
SEVERE	Mean		529.18	10.674
	95% Confidence Interval for Mean	Lower Bound	506.55	
		Upper Bound	551.81	
END-STAGE	Mean		519.30	6.378
	95% Confidence Interval for Mean	Lower Bound	506.08	
		Upper Bound	532.53	

Linear regression estimator in these patients predicted that thinner CCT were likely to have more severe form of visual field changes compared to thicker CCT (p = 0.013). (Figure 1)

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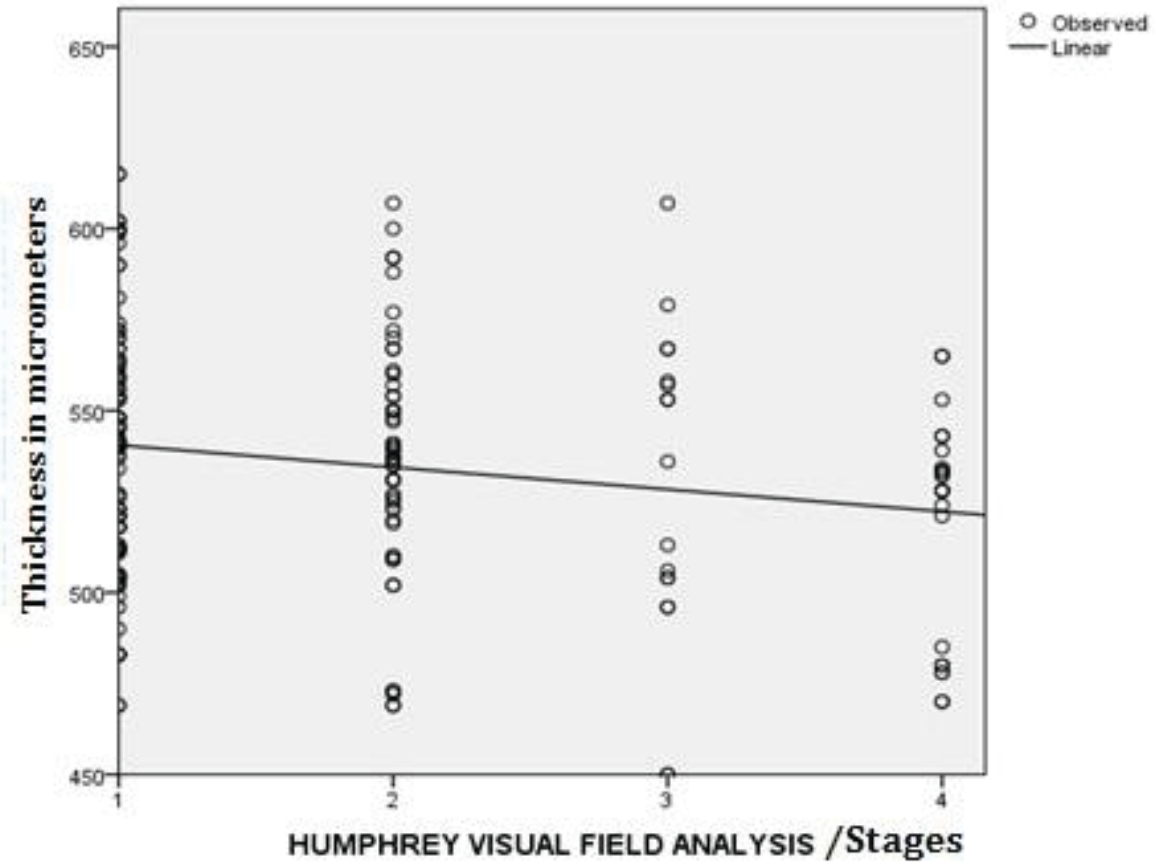

Model Summary				
R Square	F	df1	df2	Sig.
.033	6.305	1	336	0.013

Fig. 1: Severity of visual field defect and its relation with central corneal thickness in glaucoma patients without diabetes (Legend X-axis 1. Mild, 2. Moderate, 3. Severe, 4. very Severe/end stage)

We also analyzed if thinner corneas had a more severe form of glaucomatous optic disc changes in term of cup disc ratios. Linear regression estimator showed that thinner CCT also had a more severe form of optic disc changes compared to thicker CCT ($p = 0.037$). (Figure 2)

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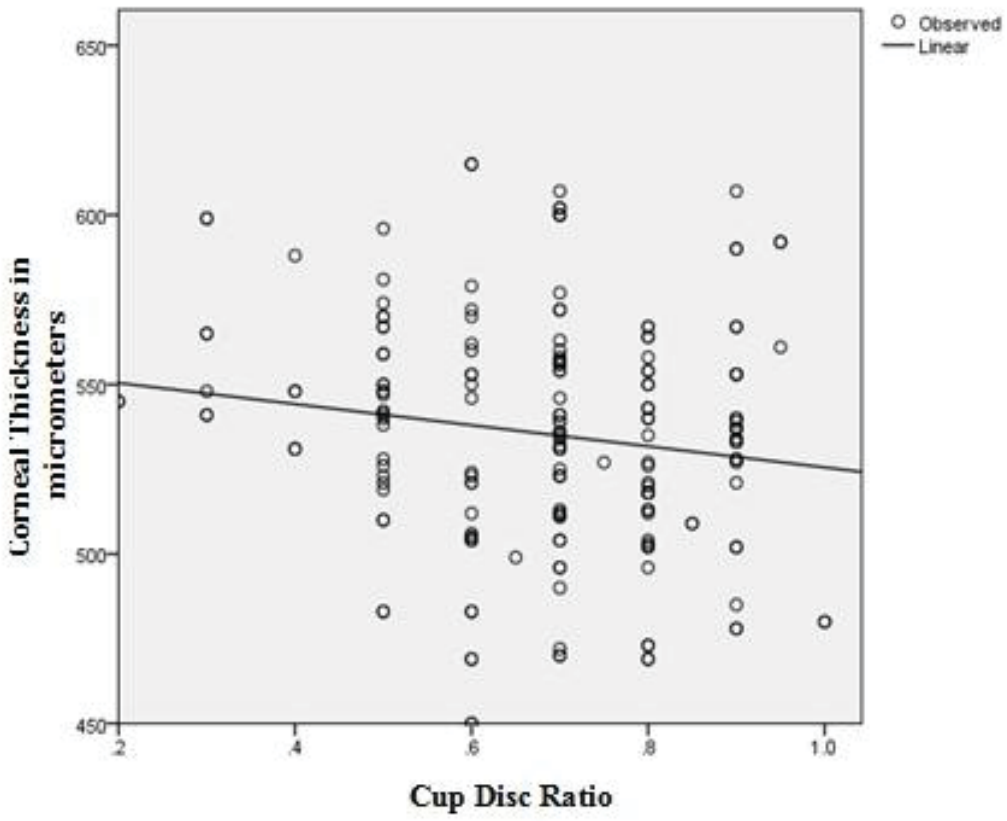

Model Summary				
R Square	F	df1	df2	Sig.
.023	4.417	1	336	0.037

Fig. 2: Severity of optic disc changes and its relation with central corneal thickness in glaucoma patients without diabetes.

CCT IN POAG PATIENTS WITH DIABETES AND ITS PREDICTIVE VALUE

Two hundred and fifty patients with POAG and diabetes were evaluated for their CCT and its correlation with severity. This group of patients had a mean corneal thickness of 549±20.2µm.

The details of the findings are illustrated in Table 2. CCT and visual field changes did not seem to agree with the general consensus.

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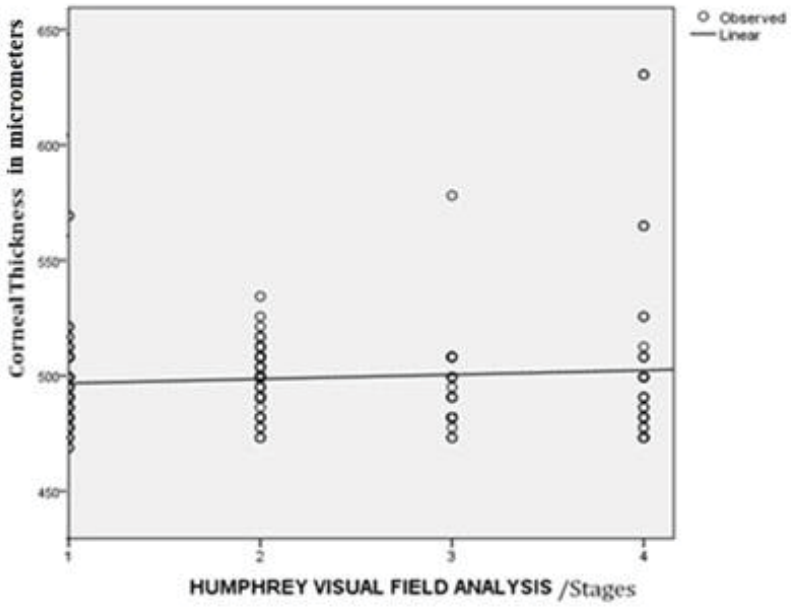
Table 2: Severity of VFD in patients with POAG with Diabetes mellitus and analysis with the CCT

HUMPHREY VISUAL FIELD ANALYSIS			STATISTICS	STD.ERROR
MILD	Mean		535.50	4.26
	95% Confidence Interval for Mean	Lower Bound	519.68	
		Upper Bound	551.32	
MODERATE	Mean		555.93	5.85
	95% Confidence Interval for Mean	Lower Bound	542.38	
		Upper Bound	569.48	
SEVERE	Mean		561.00	11.9
	95% Confidence Interval for Mean	Lower Bound	491.95	
		Upper Bound	574.85	
END-STAGE	Mean		545.00	7.83
	95% Confidence Interval for Mean	Lower Bound	518.84	
		Upper Bound	551.91	

We also analyzed if CCT in diabetic patients followed the general agreement that thinner corneas have a more severe form of glaucomatous visual field and optic disc changes. Linear regression estimator of both the parameters failed to agree with the expected relationship.(Figure 3 and Figure 4) Both demonstatedthat CCT had poor predictive value for severity of POAG in diabetic patients - p = 0.640 and p = 0.826 respectively.



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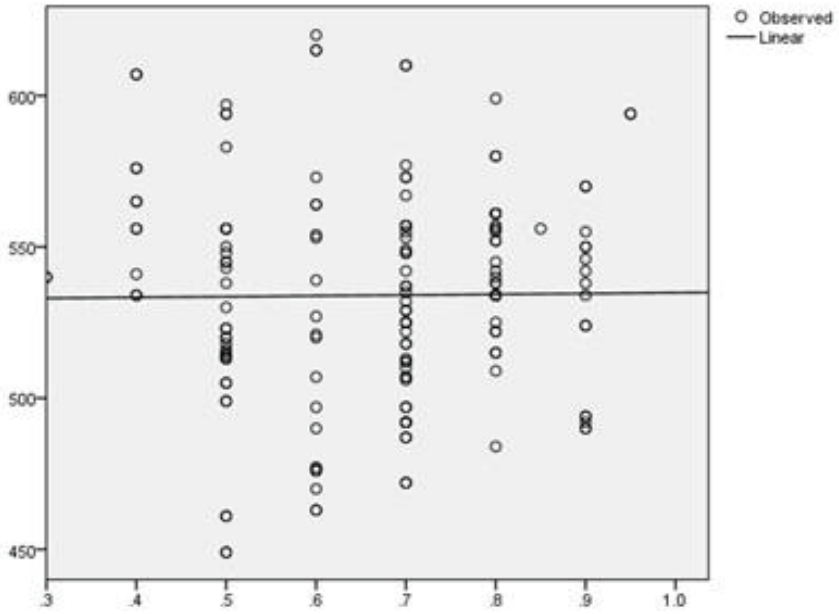
Model Summary				
R Square	F	df1	df2	Sig.
.008	.224	1	249	0.640

Fig. 3: Severity of visual field changes and its relation with central corneal thickness in glaucoma patients with diabetes (Legend X-axis 1. Mild, 2. Moderate, 3. Severe, 4. very Severe/end stage)



Model Summary				
R Square	F	df1	df2	Sig.
.002	.051	1	249	.824

Fig. 4: Severity of optic disc changes and its relation with central corneal thickness in glaucoma patients with diabetes.

Comparison of severity predictability of CCT in POAG patients with and without diabetes.

Using the linear regression values, we categorized the patients with diabetes according to their HbA1c levels and evaluated the mean CCT in each of the group. The mean resultant CCT was used as a comparison parameter among two groups to determine what severity it corresponded to (Table 3).The CCT was found to be thicker in diabetic with higher HbA1c levels and found to be not correlating to expected outcomes. CCT of 528.75 microns in diabetic patient was corresponding to a milder form of POAG while a patient without diabetes with similar value of CCT were found to have more severe form of POAG.

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Table 3: CCT correspondence compared among non diabetic and diabetic patients on severity of POAG.

HbA1c Levels(gram %)(only for Diabetic Group)	6-6.4	6.5-6.9	7-7.4
Average CCT In Diabetic Group (µm) (Corresponding CCT) (95% CI, p<0.05)	528.75±11.8µm	547.1±19.5µm	565.7±27.2µm
Visual Field Defect for Corresponding CCT for Diabetic Group	Mild	Mod- Severe	Mod- Severe
VFD for Corresponding CCT for Non - Diabetic Group	Severe	Mod-Mild	Mild
CDR for Corresponding CCT for Diabetic Group	0.61	0.58	0.64
CDR for Corresponding CCT for Non- Diabetic Group	0.98	0.88	0.82

DISCUSSION

It is a very well established finding that POAG patients with advanced disease have significantly thinner corneas. This has been recorded in many studies.[8,22,23] The inverse correlation between CCT and VF stage underlines the importance of taking into consideration the corneal thickness in the long-term strategy of treatment of POAG.[24,25] Various studies have also evaluated that thinner CCT is associated with more profound optic disc changes [26,27]

However, it is now known from various studies that the patients with diabetes have thicker corneas.[16, 24] Endothelium pump dysfunction or increased deposition of glycosaminoglycan in the cornealstroma or both are some of the many proposed mechanisms.This could mean that CCT measurements can be confounded and hence cause it loses its predictability value in detecting the severity of POAG.

We evaluated if the CCT still retains its predictability as a risk factor and severity in POAG patients with diabetes. To our knowledge, various studies have evaluated and established the fact that patients with diabetes have thicker corneas but none has evaluated if this correlation confounds the predictive value of CCT of POAG patients with diabetes. Our study supports the expected outcome/ finding cased on CCT in POAG patients without diabetes that thinner corneas are at higher risk of having more severe form of POAG>.

However, the CCT measurements did not correlate with severity of POAG patients with diabetes. Our study showed that the CCT was unreliable marker in diabetic patients and tends to lose its predictability value on severity. This is possibly due to the endothelial pump dysfunction, stromal swelling due to higher glucose level and deposition of glycosaminoglycans as mentioned earlier. Patients with diabetes failed to show a correlation of severity of POAG in terms of both visual field changes and optic disc changes with their corresponding CCT. The severity of POAG which would have been normally been expected/ obtained for a particular CCT reading showed significant deviation. This denotes that CCT is greatly influenced by hyperglycemic state and while measuring a CCT as a risk factor or a predictor for severity, history of diabetes, duration and status of glycemic control must be taken into consideration.

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CONCLUSION

CCT values may not retain its predictive value for a risk factor/severityof POAG in patients with diabetes. Hence, CCT alone may not be a reliable marker and mislead treating physicians. Diabetes should always be ruled out and a meticulous examination of both visual field changes and optic nerve head changes should be done irrespective of the CCT measurements in patients with diabetes.

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