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Central corneal thickness and optic disc changes in type-2 diabetes mellitus with diabetic retinopathy - A prospective cross-sectional study in a tertiary care centre

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Abstract: *Background:* Diabetes Mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. It becomes a global epidemic and day by day it is increasing, expecting more than 200 million type 2 DM cases will be seen in next decade predicted by World Health Organization (WHO). India has 31.7 million diabetic patients and the number is expected to increase upto 79.4 million by 2030. Diabetic retinopathy (DR) remains a leading cause of visual disability and blindness. It is a major microvascular complication of diabetes and is frequently accompanied by lipid exudation. The elevated level of blood glucose and HbA1c is highly associated with changes in central corneal thickness. *Objective:* To estimate the changes of central corneal thickness (CCT) and optic disc in type-2 diabetes mellitus patients with or without retinopathy. *Materials and Methods:* It was a hospital base cross sectional study. The study population were selected according to inclusion and exclusion criteria after proper evaluation. The study population was divided into two groups. Group A *(control)* and group B *(study)* were considered as patients who had type 2 DM without DR and with DR respectively. The data were collected and tabulated in excel sheet. The statistical analysis was done as percentage, proportion Pearson's chi square test/ Mann-Whitney U test. The statistical significant was considered if p value < 0.05. *Results:* The mean CCT of control and study groups were 549.60±4.56µm and 555.45 ± 5.71µm respectively. ($p \leq 0.001$). The mean IOP of control and study groups were 19.88±1.82 mm Hg and 23.55 ± 1.77 mm Hg respectively. ($p \leq 0.001$). Among study groups, optic atrophy, disc hemorrhage, disc neovascularization (NVD) and nerve fiber damage were 4%, 2%, 4% and 4% respectively. *Conclusion:* The Type2 diabetes with retinopathy patients had higher CCT, increase risk of optic atrophy, NVD and nerve fiber damage.

Keywords: Central Corneal Thickness (CCT), Diabetic Retinopathy (DR), Diabetes Mellitus (DM), Optic disc.

Introduction

Diabetes Mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of D M are caused by a complex interplay of genetics and environmental factors. Depending on the etiology of the DM, factors contributing to hyperglycemia include reduced insulin secretion, inefficient insulin action or decreased glucose utilization, and increased glucose production. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system.

Diabetes Mellitus becomes a global epidemic and day by day it is increasing, expecting more than 200 million type 2 DM cases will be seen in next decade [1] predicted by World Health Organization (WHO). India has 31.7 million diabetic patients and the number is

expected to increase upto 79.4 million by 2030 [2]. Diabetic retinopathy (DR) remains a leading cause of visual disability and blindness. It is a major microvascular complication of diabetes and is frequently accompanied by lipid exudation [3]. The elevated level of blood glucose and HbA1c is highly associated with changes in central corneal thickness [4]. Dyslipidemia leads to the development of hard exudates and Clinically Significant Macular Edema (CSME). These, in turn, interfere with vision [5].

High blood glucose for long-duration causes thicker central cornea. Several studies have found that Diabetes is a risk factor for primary open-angle glaucoma [6]. In this regard, central corneal thickness (CCT) has also been demonstrated to be associated with the onset and progression of glaucoma. Moreover, thicker or thinner central corneas may lead to either overestimation or underestimation of intraocular pressure (IOP) [7] which is the most important causal and treatable factor for glaucoma. This is so for especially eyes with CCT greater than 550 micrometers; every 10 µmicrometer increase in CCT was associated with 0.32 mm Hg changes in IOP [8]. Taken together accurate determination of CCT is important in the context of glaucoma diagnosis and management. High blood glucose also causes visual defects or blindness by affecting the optic disc. High blood glucose for long period causes vascular occlusion, retinal ischemia and subsequent release of vasoproliferative factors may lead to DR [9].

There are few clinical manifestations of optic nerve damage related to DM and DR that can be observed. Those are swelling of the optic disc (diabetic papillopathy), neovascularization of optic disc, and optic nerve atrophy [9]. Patients with DR are 25 times more likely to become blind than non-diabetics. In diabetes mellitus, there is an alteration in carbohydrate and protein metabolism due to the development of microvascular and macrovascular complications which have a significant impact on the quality of life and result in a substantial increase in morbidity and mortality.

Aims and objectives:

1. To study the changes in central corneal thickness in patients with Diabetic Retinopathy.
2. To evaluate the changes of the optic disc in patients with type-2 Diabetes Mellitus having Retinopathy.
3. To evaluate the risk of Primary Open-Angle Glaucoma in patients with type2 Diabetes Mellitus having Retinopathy associated with changes in CCT and Optic disc.

Material and Methods

Study design: it was institutional based cross-sectional study.

Study period: 12 months.

Study setting and time lines: 1st June 2019 to 31st May 2020.

Place of study: Calcutta National Medical College & Hospital, Kolkata, West Bengal.

Study population: All consecutive diabetes mellitus patients attended outpatient department (OPD) and eye emergency, department of Ophthalmology, Calcutta National Medical College &Hospital, Kolkata were selected according to inclusion and exclusion criteria after proper evaluation.

The patients were divided into two groups:

- *Group –A (Control):* Patients with type2 Diabetes mellitus without retinopathy and
- *Group –B (Study):* Patients with type 2 Diabetes mellitus with retinopathy.

Sample size: It was as per required for obtaining statistical significance using prevalent rates for a cross sectional population. It was a minimum of 150 patients (dividing into two groups).

Inclusion criteria: All patients attended the out-patient department (OPD) and eye emergency, willing to participate in the study and diabetic patients with or without diabetic retinopathy either in one or both eyes.

Exclusion criteria: All patients who had history of intraocular surgery, history of intraocular injection, gestational diabetes, history of cerebrovascular accident (CVA), history of hypertension and patients with major comorbidities like–Chronic kidney disease, CKD/ Cushing's syndrome were excluded from the study.

Case definitions: Diagnosis of the central corneal thickness, general optic disc and glaucomatous disc changes were done with non-contact tonometer (NCT), indirect ophthalmoscope and optical coherence tomography (OCT) respectively in type-2 DM with or without retinopathy at the time of presentation and subsequent follow up.

Study variables: Central corneal thickness, general optic disc and glaucomatous disc changes in type-2 DM with or without retinopathy.

Study tools: Following were the study tools required to evaluate the patients: Flash torchlight, Slit Lamp, Direct Ophthalmoscope, Indirect Ophthalmoscope, +20D lens, +90D lens, BP Machine, Auto refractometer, 2% fluorescent strip, Gonioscope, Applanation Tonometry, Non-Contact Tonometer, Visual field analyzer and Optical Coherence Tomography machine (OCT).

Slit-lamp examination: Detailed examination was done to note the status of conjunctiva, cornea, anterior Chamber, iris, and lens. Any atrophic patch on the iris and signs of exfoliation were noted. Pupillary reaction was noted. The depth of the anterior chamber was assessed by van-Herrick method.

Tonometry: The cornea was anesthetized using 0.5 percent proparacaine eye drop. The tear film was stained with sodium fluorescein 2%, and IOP was then measured using an Applanation Tonometer ("Goldman" model, Haag-Streit, Bern, Switzerland). The IOP was measured three times in quick succession in each eye, and the IOP was taken as the mean of the three readings.

Gonioscopy: Gonioscopy was performed in a routine manner using the Goldman two-mirror Gonioscope to evaluate the angle status. Gonioscopy was done with adequate illumination with the patient looking straight ahead; special care was taken to ensure that the slit beam did not encroach upon the pupillary area during this procedure. Next, the patient was instructed to look in the direction of the mirror and the angle manipulated open to look for synechiae

Fundus Examination: Optic disc was examined after dilating each pupil with one drop of a mixture of tropicamide 0.8% and phenylephrine 5%. Slit lamp bio -microscopy with+ 90D lens (volk) and indirect ophthalmoscopy were done to evaluate glaucomatous and diabetic optic disc changes in type 2 diabetes mellitus with or without retinopathy.

Optical coherence tomography: RNFL thickness around optic disc was determined by OCT 3000 (V4.2.4 Zeiss-Humphrey, Dublin, California, USA) after dilatation of pupil with one drop of a mixture of tropicamide 0.8% and phenylephrine 5%.

Statistical Analysis: The data were collected and tabulated in excel sheet. The statistical software SPSS version 20 was used to analyze the data. The statistical analysis was done as percentage, proportion Pearson's chi square test/ Mann-Whitney U test. The statistical significant was considered if p value < 0.05.

Categorical variables were expressed as the number of patients and the percentage of patients and compared across the groups using Fisher's Exact Test. While continuous variables were expressed as Mean, Median, and Standard Deviation and compared across the groups using the Mann-Whitney U test/ Kruskal Wallis Test as appropriate.

Results

The study was male preponderance (56%). Most of the patients had the disease less than 5 years duration. 2%,4% and 4% patients had slinter hemorrhage, neovascularization and RNFL loss respectively. Most of the patients had pink color disc (96%). The central corneal thickness (CCT), intra ocular pressure (IOP), cup-disc ratio and central macular thickness (CMT) changes were statistically significant with duration of disease ($p < 0.001$) (Table-1).

The central corneal thickness (CCT), intra ocular pressure (IOP), cup-disc ratio and central macular thickness (CMT) changes were statistically significant in DR and in poorly glycemic controlled patients (HbA1c level > 7%) ($p < 0.001$). Color changes of the disc was statistically significant with duration of disease ($p<0.001$) and in diabetic retinopathy respectively (Table-2)) ($p<0.028$) Splinter hemorrhage and neovascularization in the fundus were found statistically significant

with increased duration of the disease. (p<0.001) (Table-3) RNFL damage was found significantly with long duration of DM (P<0.001) as well as in diabetic retinopathic changes. (p<0.012) (Table-4) Significant RNFL damage was seen in diabetic retinopathy in poorly glycemic controlled patients (HbA1c level >7%). (p<0.004) (Table-5).

Table-1: CCT, IOP, VCDR, and CMT changes according to the duration of DM.

Duration of DM year		CCT (µm)	IOP (mm Hg)	OD-Vertical Cup Disc Ratio	CMT (µm)
<5	Mean	549.88	19.93	0.38	296.89
	Median	549.00	20.00	0.40	290.00
	Std. Deviation	4.55	1.70	0.07	14.74
5-10	Mean	555.02	23.57	0.42	319.13
	Median	556.00	24.00	0.40	320.00
	Std. Deviation	5.71	1.38	0.07	26.33
>10	Mean	557.90	24.95	0.52	348.40
	Median	559.00	25.00	0.50	326.00
	Std. Deviation	5.58	1.05	0.12	44.60
	p Value	<0.001	<0.001	<0.001	<0.001
	Significance	Significant	Significant	Significant	Significant

Kruskal Wallis Test showed significant changes in CCT, IOP, VCDR, and CMT in diabetic retinopathy patients according to the duration of diabetes mellitus

Table-2: CCT, IOP, VCDR, and CMT changes according to the HbA1c level and with or without diabetic retinopathy

HbA1c %		CCT (µm)	IOP (mm Hg)	OD-Vertical Cup Disc Ratio	CMT (µm)
<7	Mean	550.16	20.37	0.37	294.19
	Median	549.00	20.00	0.40	290.00
	Std. Deviation	4.88	2.14	0.07	11.24
>=7	Mean	555.70	23.52	0.46	332.61
	Median	556.00	24.00	0.45	326.00
	Std. Deviation	5.74	1.91	0.10	33.29
	p Value	<0.001	<0.001	<0.001	<0.001
	Significance	Significant	Significant	Significant	Significant
DR					
NO	Mean	549.60	19.88	0.37	290.57
	Median	548.00	19.00	0.40	290.00
	Std. Deviation	4.54	1.82	0.07	4.49
YES	Mean	555.45	23.55	0.45	330.59
	Median	556.00	24.00	0.40	325.00
	Std. Deviation	5.71	1.77	0.09	31.45
	p Value	<0.001	<0.001	<0.001	<0.001
	Significance	Significant	Significant	Significant	Significant

Mann-Whitney U Test showed significant changes in CCT, IOP, VCDR, and CMT according to the HbA1c level and DR patients.

Table-3: Distribution of patients with splinter hemorrhage and neovascularization according to the duration of diabetes						
		Duration of DM in year			Total	p Value
		<5	5-10	>10		
OD-Splinter hemorrhage's	NO	84(100)	46(100)	17(85)	147(98)	<0.001
	YES	0(0)	0(0)	3(15)	3(2)	
Total		84(100)	46(100)	20(100)	150(100)	
OD-Neovascularization	NO	84(100)	46(100)	14(70)	144(96)	<0.001
	YES	0(0)	0(0)	6(30)	6(4)	
Total		84(100)	46(100)	20(100)	150(100)	
Fisher's Exact Test showed a significant correlation of optic disc neovascularization in diabetic retinopathy patients according to the duration of diabetes mellitus						

Table-4: Distribution of patients with RNFL damage according DR and the duration of DM					
RNFL thickness changes	DR			Total	p Value
	NO	YES			
NORMAL	75(100)	69(92)		144(96)	0.012
ABNORMAL	0(0)	6(8)		6(4)	
Total	75(100)	75(100)		150(100)	
OCT-RNFL	Duration of DM in yrs.				
	<5	5-10	>10		
NORMAL	84(100)	46(100)	14(70)	144(96)	<0.001
ABNORMAL	0(0)	0(0)	6(30)	6(4)	
Total	84(100)	46(100)	20(100)	150(100)	
Fisher's Exact Test showed significant RNFL damage in diabetic retinopathy patients according to the duration of diabetes mellitus					

Table-5: Distribution of patientswith RNFL damage according to the HbA1c level				
RNFL thickness changes	HbA1c		Total	
	<7	>=7		p Value
NORMAL	86(100)	58(90.63)	144(96)	0.004
ABNORMAL	0(0)	6(9.38)	6(4)	
Total	86(100)	64(100)	150(100)	
Fisher's Exact Test showed significant RNFL damage in diabetic retinopathy patients according to the HbA1c level.				

Discussion

The present study was conducted in a tertiary care teaching institute. This was a cross-sectional study done to evaluate the changes in central corneal thickness and optic disc in type-2 diabetes mellitus patients and to prove that diabetic retinopathy is a risk factor for developing primary open-angle glaucoma. The present study showed that CCT changes was significantly correlated in diabetic retinopathy in comparison to diabetes without retinopathy. The mean CCT was 549.60 ± 4.54 µm and 555.45 ± 5.71 µm in without DR and DR patients respectively ($p \leq 0.001$). It was

thicker in DR than in diabetes without retinopathy.

Zengin et al [4] showed that CCT was significantly higher in diabetic patients than in non-diabetic subjects. Diabetic patients with HbA1c levels over 7% had thicker corneas than patients with HbA1c levels under 7% (P = 0.021). In this study, IOP change was statistically significant in DR in compare to diabetes without retinopathy. The mean IOP was 23.55 ± 1.77 mm Hg and 19.88±1.82 mm Hg in DR and without DR respectively. ($p \leq 0.001$).

Ozdamar et al [7] reported that the central cornea of diabetic patients is thicker when compared with nondiabetic patients. They also reported that thicker central cornea associated with diabetes mellitus should be taken into consideration while obtaining accurate intraocular pressure measurements in diabetics.

Wei et al [8] conducted a study to determine the distribution and relation of central corneal thickness (CCT) and intraocular pressure (IOP) by NT-530P in Chinese juveniles, and the effect of gender, age, height, weight and refractive errors on the CTT and IOP. The mean CCT and IOP were 554.19 ± 35.46 µm and 15.31 ± 2.57 mmHg respectively. There were significant correlations between the CCT and IOP values. Linear regression analysis revealed a positive correlation between CCT and IOP ($r=0.44$, $P<0.05$). The present study showed that a significant disc changes such as disc neovascularization, optic atrophy and splinter hemorrhage was found in diabetic retinopathy patients. The study proved that disc changes was increased with increased duration of diabetes in diabetic retinopathy.

Victor et al [9] conducted a study to evaluate disc changes in diabetes with DR. There were few clinical manifestations of optic nerve changes in DR such as diabetic papillopathy, neovascularization of optic disc, and optic nerve atrophy. The present study showed that a significant reduction of RNFL was found in diabetic retinopathy in compared to diabetes without retinopathy. ($p<0.012$) Type2 diabetes mellitus with poor glycemic control for long duration, had a high chance of developing optic atrophy, optic disc neovascularization, and RNFL damage as a sign of diabetic retinopathy. ($p<0.004$ & $p<0.001$)

Konigsreuther [10] performed a study to evaluate the diabetic changes of the optic disc. Their study showed that there was reduced visibility of RFNL and increased optic disc pallor without neuro-retinal rim changes suggest non-glaucomatous nerve atrophy in diabetic eyes. Our study showed that a significant change was found in CCT, IOP and loss of retinal nerve fiber layer in DR in comparison to diabetes without retinopathy. Quadrantic RNFL thickness (inferotemporal) changes was noticed in diabetic retinopathy. All findings of diabetic retinopathy had increased the risk of primary open-angle glaucoma.

Bonovas [6] conducted a study to prove the association of diabetes mellitus with primary open-angle glaucoma. The association of diabetes mellitus with primary open- angle glaucoma was statistically significant assuming either a random-effects [OR = 1.50, 95% confidence interval (CI) 1.16, 1.93], or a fixed - effects model (OR = 1.27, 95% CI 1.10, 1.45). Their meta - analysis results suggest that diabetic patients are at significantly increased risk of developing primary open-angle glaucoma.

Chopra [11] undertook a study to rule out the relationship between type 2 diabetes mellitus (T2DM) and the risk of developing open-angle glaucoma (OAG) in an adult Latino population. The prevalence of OAG was 40% higher in participants with T2DM than in those without T2DM (age/gender/intraocular pressure–adjusted odds ratio, 1.4; 95% confidence interval, 1.03–1.8; P = 0.03). Trend analysis revealed that a longer duration of T2DM (stratified into 5-year increments) was associated with a higher prevalence of OAG ($P<0.0001$).

Mitchell [12] conducted a study to explore the relationship between diabetes and open-angle glaucoma in a defined older Australian population. Glaucoma prevalence was increased in people with diabetes. Diabetes was present in 13.0% of people with glaucoma, compared to 6.9% of those without

glaucoma. The significant and consistent association between diabetes and glaucoma was found in our study.

Conclusion

The present study demonstrated that a significant correlation of CCT, IOP, optic disc neovascularization, optic atrophy, and retinal nerve fiber layer damage was seen in diabetic retinopathy in comparison to diabetes without retinopathy. Type-2 DM with poor glycemic control for long duration, had a high chance of developing optic atrophy, optic disc neovascularization, and RNFL damage as a sign of diabetic retinopathy. This study showed that type-2 DM with retinopathy had high CCT, and IOP measurement. Above findings proved that diabetic retinopathy was a risk factor for developing primary open-angle glaucoma.

Limitation of the study: A large sample size and long duration of study are required to establish strong relationship between primary open-angle glaucoma and diabetic retinopathy. If it is proved, current treatment guidelines of primary open-angle glaucoma may be changed and improving quality of life.

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