Central Corneal Thickness and Intraocular Pressure in Type II Diabetes

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ABSTRACT
Background: Diabetes is a rapidly-growing global health problem with a significant impact on morbidity and mortality due to diabetes-related complications. **Objective:** The purpose of this study was to assess the impact of type II diabetes on the central corneal thickness (CCT) and intraocular pressure (IOP). **Patients and Methods:** This prospective case-control study was performed at the ophthalmic department of Al-Zahraa University Hospital. It was conducted on 30 participants with type II diabetes and 10 healthy control (both eyes were included). Diabetics were categorized into 3 groups, diabetics without retinopathy, with non-proliferative diabetic retinopathy (NPDR) and with proliferative diabetic retinopathy (PDR).Each group contained 10 participants. Complete ophthalmic examination was done for all participants including, visual acuity, slitlamp, fundus examination, measurement of IOP and CCT. Fundus photography and measurement of glycosylated hemoglobin A1c (HbA1c) were done for diabetics. **Results:** Diabetics with PDR exhibited significantly higher IOP and CCT values compared to other groups. The IOP was significantly correlated with CCT and with the duration of diabetes.
Conclusion: Diabetics with PDR had a significantly elevated IOP and thicker corneas than normal subjects. These data emphasize the importance of considering CCT measurements in diabetics for proper interpretation of IOP.
Keywords: intraocular pressure, type II diabetes, central corneal thickness.

INTRODUCTION
Diabetes mellitus (DM) is a chronic metabolic disorder associated with hyperglycaemia, andcaused by defect in insulin secretion and/or action. An increasing prevalence of DM is occurring worldwide especially in developing countries.The highest DM burden is concentrated in low-income and middle-income countries[1-5].Patients with type II diabetes constitute more than 70 % of all diabetic patients worldwide and represent a growing epidemic[2,4,6].Currently, the prevalence of type II diabetes in Egypt is about 15.6% of adults aged between 20 and 79 years. The International Diabetes Federation (IDF) has identified Egypt as the ninth country in the world with the highest number of type II diabetic patients[6]. Diabetes causes long-term systemic complications that have considerable impact on the patient as well as the society [3,4].

The disease is divided into two main types: type I and type II diabetes. Type I diabetes is an autoimmune disease in which the β-cells of the pancreas do not produce sufficient insulin resulting in absolute insulin deficiency.Type II DM is thought to be induced by complex interaction between genetic together with environmental factors. It is caused by insulin resistance in peripheral tissues and/or an insulin secretory defect of the β-cell [2,4,6].

Diabetic patients often develop ophthalmic complications, such as corneal abnormalities, iris neovascularization, glaucoma, cataracts and diabetic retinopathy (DR)[7].Primary open angle glaucoma (POAG) is the commonest type of glaucoma in diabetic patients, [8]however the relationship between diabetes and POAG is still controversial[9,10].The gold standard instrument for intraocular pressure (IOP) measurement is the Goldmann applanation tonometer[11]. However, it is calibrated assuming a "standard" corneal thickness of 500 µm (based on white populations) and hence corneal thickness would have some effect on the measured IOP values. Thicker or thinner corneas may lead to either overestimation or underestimation of IOP, respectively. The extreme of error has a wide range of almost12 mm Hg. As a result, various correction methods have been proposed[12-13].

Objective: The purpose of this study was to assess the impact of type II diabetes on the central corneal thickness (CCT) and intraocular pressure (IOP).

SUBJECTS AND METHODS
This prospective case-control study was conducted from July 2018 to January 2019 at the ophthalmology department of Al-Zahraa University Hospital.

Approval of the Ethics Board of Al-Azhar University was obtained and the study adhered to the principles of the Declaration of Helsinki guidelines. A written informed consent was taken from all the subjects after full explanation.

Forty participants, aged between 40 and 60 years, were enrolled into the study; both eyes were included. They were divided into 30 patients with type II diabetes compared to 10 age matched healthy

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persons (control group). Diabetics were further subdivided into: diabetics without retinopathy, with non proliferative diabetic retinopathy and with proliferative diabetic retinopathy. Each group contained 10 participants. The diagnosis of DM was established by an internist.

Exclusion Criteria

Ocular exclusion criteria: dense media opacities such as corneal dystrophies or degenerations, pterygium, history of uveitis, pseudoexfoliation syndrome, previous history of anti-glaucomatous treatment, ocular trauma, previous intraocular surgeries or laser therapy. Subjects who had refractive surgery or any posterior segment pathology except diabetic retinopathy were also excluded.

Systemic exclusion criteria: Type I diabetes mellitus, glycosylated hemoglobin A1c (HbA_1c) > 7 for diabetics, history of systemic disease; such as hypertension, cardiovascular diseases, renal insufficiency or any systemic diseases or medications affecting the eyes.

Examination protocol and study Measurements

Detailed history of patients with special regard to drug history, duration of DM, and type of treatment was recorded. Complete ophthalmic examination for all subjects was done including, uncorrected and best corrected visual acuity using Landolt's ring chart, refraction and slitlamp examination. IOP was measured using Goldmann applanation tonometer (GAT) with the patient in a sitting position after instillation of anaesthesic eye drops and fluorescein strips to stain the tear film. IOP measurements were taken at around 10 a.m. for all subjects to avoid diurnal variations with only one reliable measurement recorded for each subject. Dilated fundus examination for all subjects was done with the aid of 90 D lens. DR grading was performed clinically for diabetic patients and fundus photos were taken for documentation, using Topcon TRC-50EX (Topcon Corporation, Tokyo, Japan) retinal camera. Patients identified to have PDR underwent routine gonioscopy to exclude neovascular glaucoma. Central corneal thickness (CCT) measurements were taken using AL- scan (Nidek Co. Ltd, Gamagori, Japan) optical biometer.

HbA1c was done for all diabetic patients enrolled into the study to ensure good glycemic control (HbA1c≤7). Blood samples (venous blood) were taken from the antecubital fossa, within 30 days of the ophthalmic examination.

Statistical Analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when parametric. Median with inter-quartile range (IQR) when non parametric. Percentiles was used to assess the distribution of some parameters. Also qualitative variables were presented as number and percentages.

The comparison between groups regarding qualitative data was done by using Chi-square test and/or Fisher exact test when the expected count in any cell found less than 5.

The comparison between more than two independent groups with quantitative data and parametric distribution was done by using One Way ANOVA followed by post hoc analysis using LSD test.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following:

- P-value > 0.05: Non-significant (NS)
- P-value < 0.05: Significant (S)
- P-value < 0.01: Highly significant (HS)

RESULTS

Demographic characteristics of the Study Population

This study included 80 eyes of 40 participants; divided as 20 eyes of 10 healthy non diabetic subjects (Control Group) and 60 eyes of 30 type II diabetic patients, who were further classified in 3 groups based on their retinal changes. They included, 20 eyes of 10 diabetic subjects with normal fundus, 20 eyes of 10 diabetic subjects with non-proliferative changes and 20 eyes of 10 diabetic subjects with proliferative changes. The demographic and clinical characteristics of the participants are summarized in **Table 1**. There was no statistically significant difference in age between all groups (p=0.933). The mean subject age was 51.05 ± 5.75years old. As regard to sexthere was statistically significant difference with more females in the diabetic groups; **Fig.1**.

Clinical characteristics of the Study Population

The severity of retinal signs revealed significant association with the level of IOP. There was a statistically significant difference among the four groups in terms of IOP and CCT (p=0.000) as shown in **Table1**. The IOP and CCT were highest in the PDR group (**Fig.2 and 3**) as indicated by the Post hoc analysis. A positive and highly significant correlation was observed between IOP and CCT(p=0.000; r=0.768) as shown in **Table 2** and **Fig.4**. A positive and significant correlation was observed between IOP (p=0.041) and duration of DM and also between CCT and duration of DM (p=0.031) as shown in **Table 2**.

Association between retinal findings in type ll diabetics and duration of diabetes

A statistically significant difference in the duration of diabetes was observed among diabetic groups with the longest duration in the PDR group followed by the NPDR group, whereas there was no statistically significant difference in the duration between the NPDR and PDR groups.

Table (1): Shows demographic and clinical characteristics of the study population

		Control group	Diabetic (without retinopathy)	NPDR group	PDR group	Test value	P-value
Age (years)	Mean ± SD	50.8 ± 6.55	50.3 ± 4.92	51.1 ± 7.06	52 ± 4.94	0.144•	0.933
	Range	42 – 59	41 – 58	42 – 59	43 – 60		
Sex	Female	3(30.0%)	6(60.0%)	9(90.0%)	8 (80.0%)	9.231*	0.026
	Male	7(70.0%)	4(40.0%)	1(10.0%)	2 (20.0%)		
IOP (mmHg)	Mean ± SD	14.6 ± 2.16	13.9 ± 2	14 ± 2.05	19.3 ± 2.62	27.104•	0.000
	Range	12 – 18	10 – 18	12 – 18	14 – 24		
CCT (μ)	Mean ± SD	532.95 ± 24.36	519.15 ± 21.38	533.7 ± 14.97	566.9 ± 17.66	20.750•	0.000
	Range	513 – 595	501 – 569	516 – 569	528 – 598		
Duration of DM (years)	Mean ± SD	--	6.01 ± 3.98	13.0 ± 6.68	17.2 ± 7.55	8.155	0.002
	Range	--	0.58 – 12	2 – 22	10 – 30		

Post hoc analysis

	P1	P2	P3	P4	P5	P6
Sex	0.178	0.006	0.025	0.121	0.329	0.531
IOP	0.322	0.396	0.000	0.887	0.000	0.000
CCT	0.031	0.906	0.000	0.024	0.000	0.000
Duration of DM	--	--	--	0.019	0.000	0.145

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
*: Chi-square test; •: One Way ANOVA test
P1: Control vs diabetic (without retinopathy) group
P2: Control vs NPDR group
P3: Control vs PDR group
P4: Diabetic (without retinopathy) vs NPDR group
P5: Diabetic (without retinopathy) vs PDR group
P6: NPDR vs PDR group

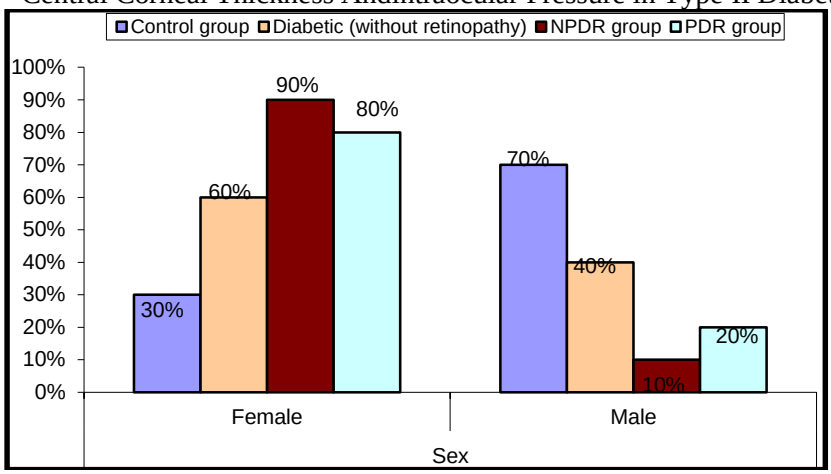

Fig.(1): Higher number of female participants in the diabetic groups

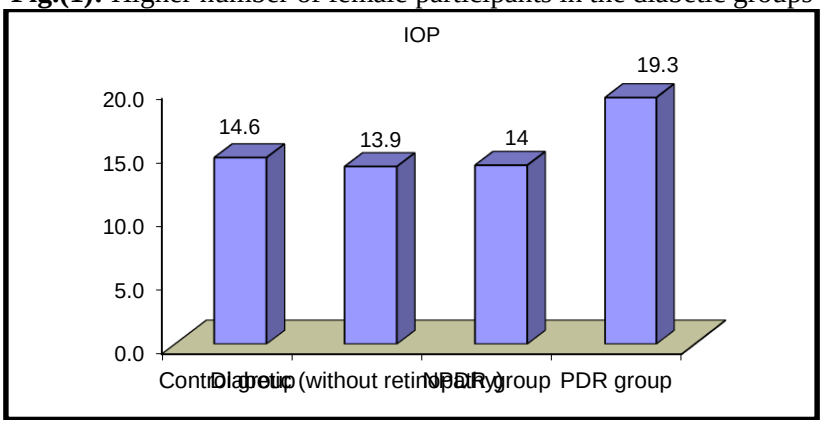

Fig.(2): IOP (mmHg) in the four groups with the highest value in the PDR group.

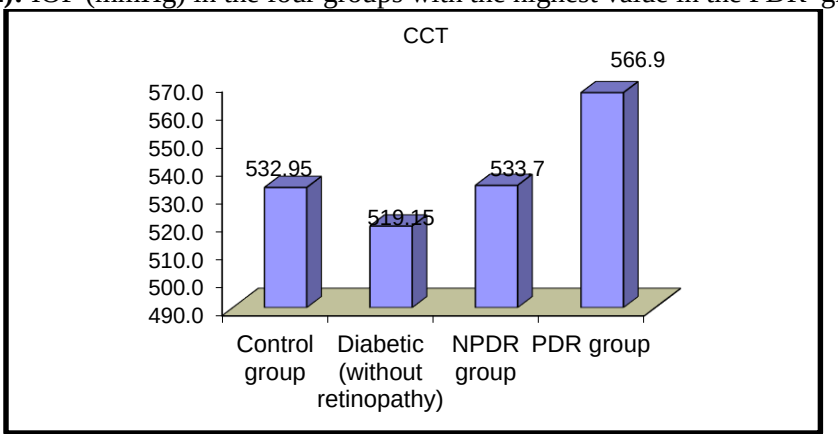

Fig.(3): CCT in the four groups with the highest value in the PDR group.

Table (2): Correlation between age, IOP, CCT and duration of DM

	Total cases					
	Age		**IOP**		**CCT**	
	r	**P-value**	**r**	**P-value**	**r**	**P-value**
Age (years)	–	–	0.147	0.366	-0.062	0.704
IOP(mmHg)	0.147	0.366	–	–	**0.768****	**0.000**
CCT(μ)	-0.062	0.704	**0.768****	**0.000**	–	–
Duration of DM (years)	0.055	0.771	0.375*	0.041	0.395*	0.031

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant, Spearman correlation coefficient

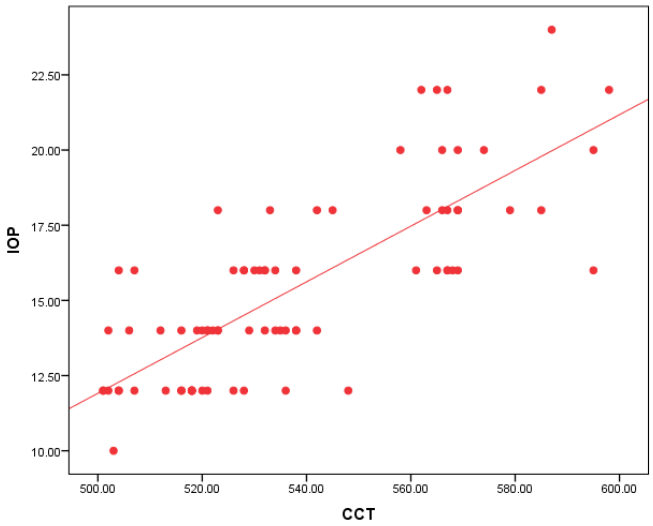

Fig.(4): Plot of IOP and CCT shows progression line representing 40 subjects (80 eyes) . This plot shows that the IOP and CCT were significantly correlated (r = **0.768**, P= 0.000, n = 80).

DISCUSSION

DM is a serious and increasingly prevalent global health problem due to increased rate of obesity caused by dietary and lifestyle changes; and also due to increased life expectancy. It can cause severe acute and chronic complications, which influence both the quality of life and survival of the affected persons in a negative way. A number of potentially vision-threatening ocular complications has been associated with DM, including diabetic retinopathy (DR), cataract, uveitis, and glaucoma.Although glaucoma is a multifactorial disease, elevated IOP remains the main known risk factor[14-17]. Some longitudinal studies have reported that the IOP is affected by systemic parameters such as diabetes, body mass index (BMI) and blood pressure (BP) levels[18-20]. The association between diabetes and elevated IOP is still controversial.A lot of population-based studies have reported that diabetes was significantly associated with higher IOP such as The Singapore Malay Eye Study[21] and the Baltimore Eye Survey[22].

The mechanism of this elevated IOP in diabetic populations is unclear, but various etiologies have been postulated such as genetic, autonomic dysfunction, and osmotic diffusion.[16,23]

In Tajimi study[24], they measured IOP (using GAT) and CCT in a random sample of 3021 Japanese participants. They reported significantly higher IOPs in diabetics (p = 0.0019), although they did not correlate this with diabetic retinopathy grading. They also reported significantly higher IOPs in individuals with thick corneas (p<0.0001).

In our study, to find the correlation between IOP and the stage of diabetic retinopathy; diabetics were classified into3 groups based on their retinal examination. The measured IOPs were compared to healthy age-matched control group. A similar study was designed by **Matsuoka et al.[11]**but they further classified diabetics with NPDR into 2 groups; group with mild to moderate NPDR and other group with severe NPDR.They found that IOP in each diabetic retinopathy group was significantly higher than that in the non-diabetic group (P< 0.001) but there was no significant difference between the diabetic retinopathy groups. In their study the highest IOP was reported in the PDR group (18.0 ± 2.2). In our study we reported a similar significantly high IOP in the PDR group only (19.3 ± 2.62); whereas there was no significant difference between other diabetic retinopathy groups and the control group unlike **Matsuoka et al.[11]** study. Different results could be explained by variable sample size, different instruments used in IOP measurement and different glycemic control.They used a non-contact tonometer while in our study we used GAT. In our study patients with HbA1c> 7 were excluded, whereas in their study they documented a significant correlation between HbA1c levels and raised IOP in diabetic patients.

There are many factors that could affect the accuracy of IOP measurements including, factors related to the measurement itself, systemic and ocular factors. Factors related to the measurement itself include, type of tonometer, the examiner and the amount of fluorescein staining. Whereas systemic factors include, dehydration and blood glucose levels.

And most importantly the ocular factors that include axial length, corneal curvature, CCT and corneal hysteresis; these last two factors are affected by DM[25-28].

Hyperglycemic environment in DM results in the formation of Advanced Glycation End Products (AGEs). They have been implicated in various harmful reactions in diabetic patients including the increased rigidity of the cornea and retinal microvascular alterations. It has also been reported that glucose with the help of AGEs can act as a collagen cross-linking agent that may lead to increased corneal thickening and biomechanical changes. [28- 30].

In a study done by **Ramakrishnan et al**. [31],they found a statistically significant increase in the corneal thickness in the diabetic group compared to the non-diabetic group. ($p = 0.000$). They also found that the corneal thickness was significantly higher in severe NPDR and PDR patients. ($p< 0.05$).

In contrast to our study; we reported that the CCT was significantly higher in PDR group only. This could be the first factor to explain the significantly higher IOP in the PDR group in our study as increased CCT might lead to overestimation of the true IOP when measured by GATespecially for eyes with CCT >550µ; in our study CCT in the PDR group was 566.9 ± 17.66. **Kohlhaas et al.**[32] stated that every 25µ increase in CCT was associated with 1 mmHg change in IOP. Second, diabetics have corneal biomechanical changes that would result in clinically relevant high IOP values apart from CCT[28].

There are several limitations of the present study. First, it is limited by its small sample size and the predominance of females in the diabetic groups (the study was age-matched but not sex-matched). Second, in our study the data was collected only once, instead of long-term follow up for observations. Therefore, longitudinal studies are needed to better understand the trend of IOP and CCT with the progression of disease in diabetic patients. Furthermore, another important factor to be addressed in future studies about IOP in diabetics is the corneal biomechanics. A cornea-compensated IOP (IOPcc) measurement provided by Ocular Response Analyzer can be used instead of GAT-measured IOP[28].

In conclusion, our study highlighted the finding that diabetics with PDR had elevated IOP and thicker corneas than normal subjects. These data emphasize the importance of considering CCT measurements in diabetics for proper interpretation of IOP.

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