Corneal Specular Microscopy Changes in Type II Diabetes Mellitus

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ABSTRACT:

BACKGROUND:

Corneal endothelial cells count and shape are vital in keeping corneal transparency with normal vision. Diabetes mellitus is associated with significant changes in the corneal endothelium.

OBJECTIVE:

To compare corneal endothelial structure and central corneal thickness (CCT) between type II diabetics and non-diabetic control patients.

METHODS:

Specular microscopy was used to measure central corneal thickness (CCT), average size of endothelial cells, standard deviation of cell size and coefficient of variation in cell area (CV), endothelial cell density, as well as hexagonality of 260 eyes from 260 patients (130 eyes from type II diabetic patients and 130 eyes from non diabetic controls).

RESULTS:

The diabetic corneas have a significant increase in average size of endothelial cells (410.4 ± 89.6 µm² vs. 382.3 ± 83.4 µm²)($p < 0.05$), standard deviation of cell size (152.2 ± 38.0 µm² vs. 128.7 ± 19.5 µm²)($p < 0.05$) and coefficient of variation (CV) (38.3 % ± 5.4 % vs. 33.4 % ± 4.4%)($p<0.05$). and a significant decrease of endothelial cell density (2570.7 ± 563.1 cells / mm² vs. 2704.1 ± 572.5 cells / mm²)($p < 0.05$) and hexagonality (48.3 ± 17.1% vs. 56.5% ±15.6%)($p<0.05$). There was no significant difference in central corneal thickness(CCT) (516.3 ± 63.4 µm vs. 512.8 ± 61.7µm)($p > 0.05$).

CONCLUSION:

Type II diabetes associated with a significant changes in the corneal endothelium including, reduction of endothelial cell density, increased variation of cells shape (pleomorphism) and increased variation of cells area (polymegathism). There was no significant changes of central corneal thickness (CCT).

KEY WORDS: corneal endothelium, central corneal thickness (CCT), specular microscopy, type II diabetes Mellitus.

INTRODUCTION:

Diabetes Mellitus, characterized by sustained hyperglycemia secondary to lack of or diminished efficacy of endogenous insulin, causes significant morbidity and mortality in multiple systems of the body.[1] The International Diabetes Federation (IDF) estimated the global prevalence of diabetes to be 285 million in 2010. This number is expected to increase by more than 50% in the next 20 years possibly reaching up to 438 million by 2030. This means approximately 7.8% of the world adult population, with 70% of cases occurring in the developing world.[2] Type II Diabetes Mellitus is the most common type of Diabetes Mellitus, constitutes about 85 to 95% of all diabetes in developed countries and may account for an even higher percentage in developing countries. The 40-59 age group currently has the greatest number of people with diabetes.[3]

The International Diabetes Federation (IDF) has been estimated the prevalence of diabetes in many countries in world but Iraq was not included.

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Most previous authors have concentrated on diabetic retinopathy, but Diabetes Mellitus can affect every part of the eye, including the cornea. Diabetes Mellitus can affect every structure of the cornea mostly epithelium and endothelium causing endothelial defects, punctate epithelial keratopathy, recurrent corneal erosions and persistent epithelial defects. [4,6]

Regarding corneal endothelial, several studies have reported that corneal endothelial cells in diabetics have morphological abnormalities. These abnormalities include a decrease in endothelial cell density and hexagonality, as well as increased polymegathism, pleomorphism and subsequently decrease in corneal endothelial function, corneal hydration and increase central corneal thickness (CCT). [7-11]

There was no reports comparing corneal state in diabetic patients and normal subjects in a sample of Iraqi population in comprehensive Medline literature search, therefore, this study was performed to investigate the effect of type II Diabetes Mellitus on corneal endothelial density, morphology and central corneal thickness (CCT) by comparing these patients with normal subjects in Ibn AL Haitham teaching eye hospital.

PATIENTS AND METHODS:

Two hundred sixty eyes were examined, 130 eyes of 130 patients aged between (50-71) years who were diagnosed with type II Diabetes Mellitus, (depending on the history and random blood sugar). Another 130 eyes of control patients were aged between (50-73) years and did not have diabetes.

In this study, only one eye of each patient was analysed. All eyes were investigated by the same specular microscopy with help of same experienced medical staff between May 12, 2013 and October 27, 2013 at Ibn AL Haitham teaching eye hospital.

Exclusion criteria included: (1) Patient of Diabetes Mellitus with duration less than 5 years (2) previous ocular surgery or trauma (3) active or previous eye infection or inflammation (4) glaucoma (5) previous retinal photocoagulation (6) contact lens wear (7) corneal disease due to chronic conjunctival or eyelid abnormalities such as extensive pterygium, entropion, trichiasis (8) regular use of any eye drops.

Pre-investigative data obtained included age, gender, history of previous ocular surgery, trauma, retinal photocoagulation, infection, inflammation, topical drug use, contact lens wear, and random blood sugar. Anterior and posterior segment examinations were performed before specular microscopy by slit-lamp biomicroscopy including intraocular pressure measurement by Goldmann applanation tonometer and air puff tonometers.

Specular microscopy was then performed using a non-contact Topcon SP-3000P (Topcon Corp, Tokyo, Japan) microscope. The captured image was analyzed with Topcon Cell Count software. Approximately 100 ±20 endothelial cells were counted in each image in the analysis. This was repeated three times for each eye and the image with the median number of endothelial cell density was used for analysis. Corneal endothelial cell density, size, standard deviation, coefficient of variation, hexagonality as well as central corneal thickness were measured.

Statistical Analyses were performed using SPSS (statistical package for social sciences) software windows version 18, and Student's independent t-test to reveal any significant association. For all the statistical tests, $p<0.05$ was taken as being significant.

RESULTS:

There were 260 patients included in this study, the patient's pre-investigated data are shown in table 1. Including age, gender, random blood sugar and duration of diabetes for diabetic patient group.

Table 1:Baseline characteristics of study group (N=360).

Variable	Diabetic pt. (N=130)	Non Diabetic pt. (N=130)
Age (years)	61.3±6.5 (50-71)	62.3±5.1(50-73)
Male	56 (43%)	63(48%)
Female	74(57%)	67(52%)
Random blood sugar	(12.4±1.3) mmol/l (222.7±23.5) mg/dl	(6.8±0.7)mmol/l (121.9 ±13.4) mg/dl
Duration of diabetes (years)	8.4±2.5 (5-18)	

By comparing with non diabetic control corneas, diabetic corneas have a significant increase in endothelial cell size, standard deviation of cell size and coefficient of variation (CV) and there is a significant decrease in endothelial cell density and hexagonality. There was no significant difference in central corneal thickness (CCT). table 2. and figures 1-6

Table 2: The difference of corneal parameters between diabetic patients and non diabetic control .

Corneal parameters	Diabetic corneas (N=130)	Non diabetic cornea (N=130)	p-value (t-test)
Average cell size	410.4±89.6 µm²	382.3±83.4 µm²	<0.01
standard deviation of cell size	152.2±38.0 µm²	128.7 ±19.5 µm²	<0.01
Coefficient of variation (CV)	38.3% ± 5.4%	33.4 % ±4.4 %	<0.01
Endothelial cell density	2570.7 ± 563.1 cells/mm²	2704.1 ± 572.5 cells/mm²	<0.01
Hexagonality	48.3%± 17.1%	56.5%±15.4%	<0.01
Central corneal thickness (CCT)	516.3 ± 63.4 µm	512.8 ± 61.7 µm	=0.28

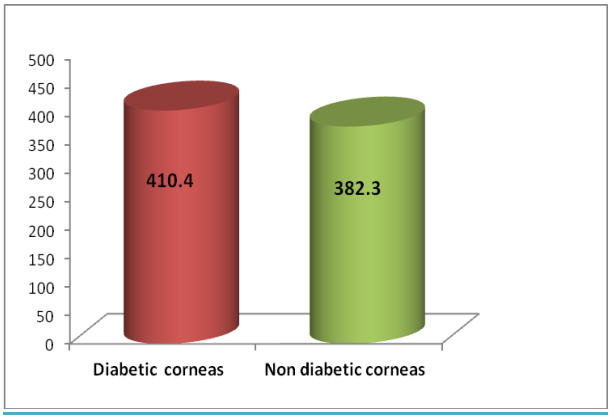

Fig .1:Average size of endothelial cells (µm²)(p<0.01).

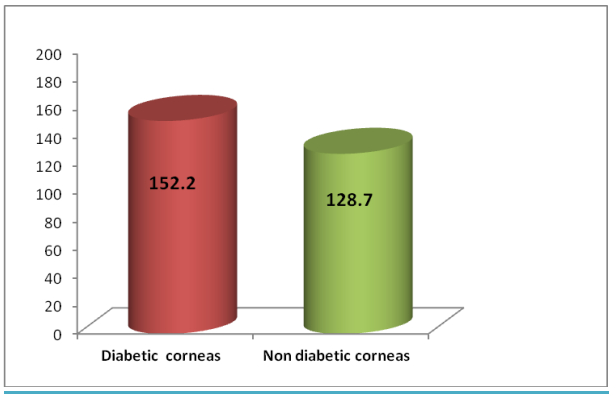

Fig .2: Standard deviation (SD) of cell size (μm²)(p<0.01).

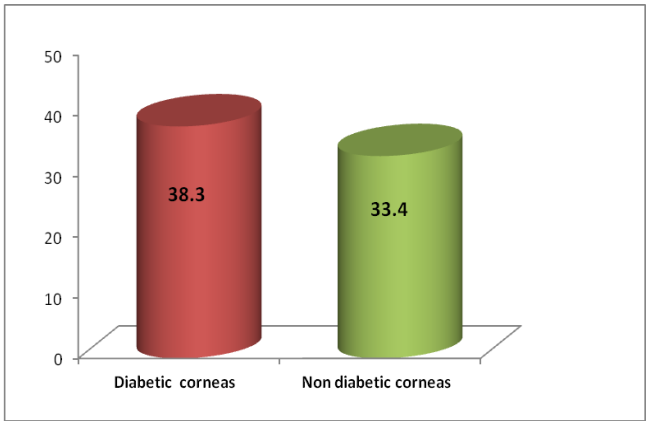

Fig.3: Coefficient of variation (CV)% (p<0.01).

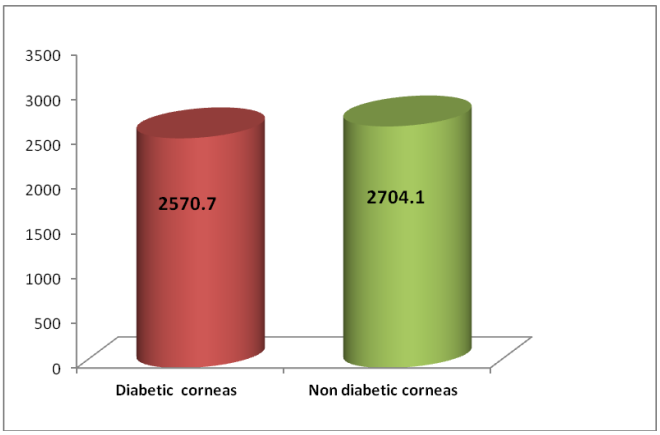

Fig.4: Endothelial cell density (cells/mm²) (p<0.01).

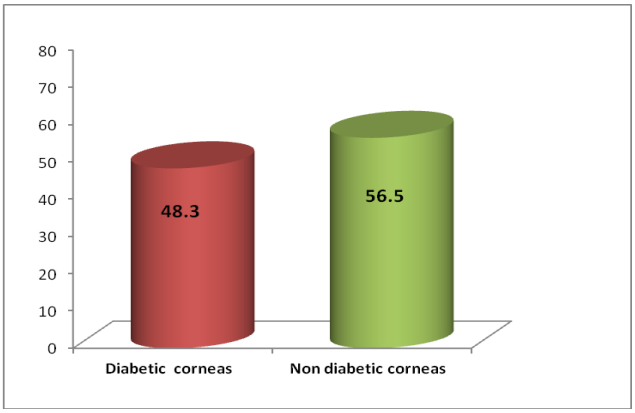

Fig.5: Hexagonality % (p<0.01).

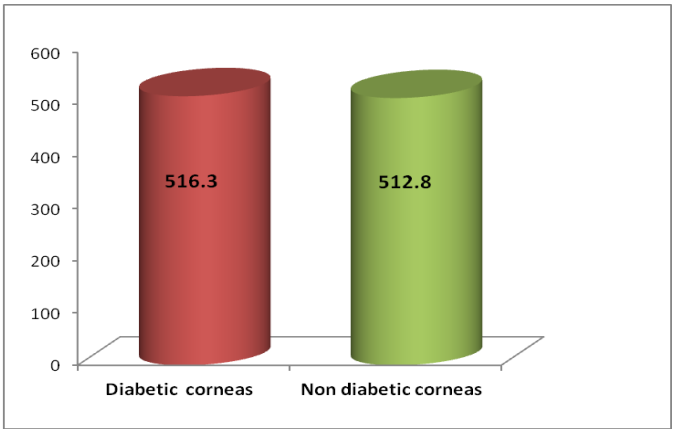

Fig.6: Central corneal thickness (CCT) (µm) (p=0.28).

DISCUSSION:

The major objectives of this study were to investigate the effect of Diabetes Mellitus on the corneal thickness and endothelial structure because corneal endothelium plays important role in maintenance of corneal transparency and various intraocular surgery outcomes depend on the state of this layer.

In this study, cornea of diabetic patients were found to be associated with statistically significant reduction in mean corneal endothelial cell density compared to control cornea. This was similar result found by Coo *et al* [7] in their study of type II diabetics in Malaysia, Inoue *et al* [8] in Japan, Shenoy *et al*[9] in Oman and Lee *et al* [10] in Korea. However, Schultz et al[11], Itoi *et al* [12] Matsuda *et al* [13] and Larsson *et al* [14] reported that in type II diabetic corneal endothelial cell density was similar to non diabetic patients.

The average size and coefficient of variation (CV) of corneal endothelial cells were found to be significantly increased in diabetics. The increase in coefficient of variation (CV) indicates the presence of polymegathism in which endothelial cells enlarge to fill the gaps between adjacent cells. This study also showed that the percentage of hexagonal cells was significantly reduced in diabetic patients, indicating the presence of pleomorphism. These results were similar to those obtained by Coo *et al* [7], Lee *et al* [10], Schultz *et al*[11] and Roszkowska *et al* [15]. However, Inoue *et al*[8] found that percentage of hexagonal cell to be not significantly different between diabetic and controls but with increase in coefficient of variation (CV). Larsson et al [14] reported that the coefficient of variation of cell area, and percentage of hexagonal cells all were not significantly different between type II diabetic and non diabetic patients.

There was no significant difference in CCT between diabetics and controls. This finding was similar to reported studies by Coo *et al* [7], Inoue *et al* [8] , Schultz *et al* [11], Larsson *et al* [14] and Siribunkum *et al* [16]. However, other studies such as by Lee *et al* [10], Roszkowska *et al* [15] and Weston *et al* [17] reported a significant increase in CCT in diabetic patients.

In all previous mentioned studies that showed results different from this study, the number of patients were enrolled was less than this study, between (70 – 92) for each diabetic and non diabetic group. Also in these studies, the maximum of cells counted in each photograph was approximately between (50-60) cells.

The exclusion criteria in these studies, were limited to only previous ocular surgery or trauma and active or previous eye infection or inflammation. These studies were included patients of short duration of Diabetes Mellitus between (6months - 22 years). Lee *et al* [10] and Skarbez et al[18] found that the effect of Diabetes Mellitus on corneal stracture increases by increase the duration of the disease. Also these studies were included patients of history of multiple sessions of retinal photocoagulation, Menchini U *et al*[19] *found that corneal endothelial density and morphology were changed after* retinal photocoagulation *through follow up between (6 weeks-6 months). Glaucoma or history of* regular use of any eye drops *was also not included in* exclusion criteria *of these studies, high IOP causes damage to the endothelial cells, its junctional barrier and pumping mechanisms, this lead to corneal edema* subsequently *increase corneal thickness (CCT*).[20] *Regular use of topical antiglaucoma drugs such as* dorzolamide may be associated with endothelial decompensation especially in patients with pre-existing corneal endothelial dysfunction [21,22,23].

In this study, the presence of polymegathism, pleomorphism and reduction in density of corneal endothelial cells in type II diabetic patients may show that diabetes affects the corneal endothelium.

There are many reports about the mechanisms of these changes in the corneal endothelial structure in diabetic patients. Aldose reductase is present in the corneal endothelium[24 ,25], the sorbitol pathway and its osmotic effects have been proposed to influence the morphological alterations of the corneal endothelium. [25,26,27]

Several experimental studies provide evidence that aldose reductase inhibitor (ARI) could be useful in changing some abnormal corneal endothelium in diabetics, Matsuda and colleagues [26] demonstrated that the topical (ARI) CT-112 decrease the reduction of endothelial cell density in diabetic rats.

Meyer and coworkers [28] in the same animal model, demonstrated that the topical (ARI) AL-1576 effectively inhibited the diabetic-associated increase in coefficient of variation (CV) and maintained relatively normal hexagonal endothelial monolayer. Datiles and associates [29] found that endothelial changes can be prevented by the use of oral sorbinil in diabetic dogs. In this regard, the clinical role of ARIs in diabetic patients has yet to be proven.

Another mechanism regarding endothelial changes that hyperglycemia can inhibit endothelial pump function by inhibiting Na^+ / K^+ ATP ase-depenent transport by induction of a locally enzyme inactivation or by inhibition of intracellular *myo*-inositol transport (a neural membrane phospholipid) and also by decreasing in the Krebs cycle with a consequent reduction in ATP production which is necessary for endothelial pump function and subsequent morphological endothelial changes.[30,31,32,33]

Kim and colleagues[34] found that the endothelial changes may be a manifestation of inadequate cell volume regulation associated with cytoskeleton abnormalities, F-actin, a major component of the cellular cytoskeleton, has a key role in the maintenance of endothelial cell shape and barrier function. They found that endothelial cells of diabetic cornea has abnormally located F-actin fibrils crossing the cytoplasm and suggested that these changes occur as a way of preventing cell rupture and subsequent loss secondary to chronic sorbitol-induced osmotic stress.

This study shows there is a difference between diabetic and non diabetic corneal endothelium, this difference may indicate that there is a higher possibility of surgical stress delayed healing following intraocular surgery, specifically cataract surgery.

CONCLUSION:

Type II diabetes associated with a significant changes in the corneal endothelium including reduction in endothelial cell density, increased variation of cells shape (pleomorphism) and

increased variation of cells area (polymegathism). There was no significant changes of central corneal thickness.

Recommendations:

This study recommend that corneal specular microscopy should be done routinely preoperatively for every diabetic patient even with normal slit-lamp corneal examination**.**

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