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SPECULAR MICROSCOPY OF CORNEAL ENDOTHELIUM IN PATIENTS WITH TYPE I DIABETES MELLITUS VERSUS NORMAL PERSONS

By

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ABSTRACT

Background: Diabetes mellitus is a general disorder that changes the main metabolic processes that distressing the functions of systems in the body. Type 1 diabetes is the generally common metabolic disorder of adulthood. Around one in each 400–600 juveniles and adults has type 1 diabetes. Its incidence has risen over new years.

Objective: To evaluate corneal endothelial alterations in type I diabetic patients with or without diabetic retinopathy.

Patients and Methods: A prospective comparative study of 60 subjects divided into two equal groups: Group A: with type I DM with or without diabetic retinopathy and Group B: normal persons matched with age and sex. All patients were subjected to full history and ophthalmic examination including Uncorrected / best corrected visual acuity (UCVA/BCVA) expressed in LogMar scoring, refraction using automated refractometer (Topcon KR-800 Auto refractometer), intraocular pressure (IOP) measurement by Goldman Applanation tonometer, Slit lamp biomicroscopy to assess corneal clarity, depth of anterior chamber, state of pupil dilatation, lens morphology, state of diabetic retinopathy in dilated pupil fundus examination and non-contact specular microscope (Topcon sp-1p, Topcon Medical Inc., Japan) to assess the corneal endothelium and patients were compared to normal persons as regard: endothelial cell density (ECD), coefficient of variation in cell size (CV), changes in percentage of hexagonal cells (HEX) and central corneal thickness (CCT). The study was done at Department of ophthalmology, Sayed Galal University Hospital, Cairo, Egypt and it was carried out from May 1st, 2019 to April 30th 2020.

Results: Among patient group, twenty one (70%) patients were females while nine (30%) patients were males. Ten persons (20 eyes) in study group were diabetics with diabetic retinopathy. There was a significant decrease in ECD, and a significant increase in CCT, also there was a significant change in CV, and HEX an increase in CV (polymegathism) and decrease in hexagonality (pleomorphism) in type I diabetic patients. Diabetic retinopathy and duration of diabetes were factors that affect central corneal thickness.

Conclusion: Cornea of a diabetic patient has lower ECD compared to normal and thicker cornea than non-diabetics also with higher coefficient of variation and lower hexagonality.

Keywords: Specular microscopy (SP), endothelial cell density, Coefficient of variation, percentage of hexagonal cells and central corneal thickness.

INTRODUCTION

Diabetes mellitus (DM) is a main worldwide human trouble, reflected by the international burden of disease study 2013 as the 9th general reason of mortality, by an approximated incidence of 8.8 % in persons aged 20-79 years *(Zheng et al., 2017).*

DM is a general disorder that changes the main metabolic processes in the body, disturbing all functions of systems. Insulin dependent diabetes mellitus (IDDM) is the widespread metabolic disorder of juvenile. Nearby one in every 400-600 kids and adolescences has type l DM. Its occurrence has risen around new years *(Misra et al., 2016).*

Long standing DM affects ocular metabolism and may lead to many complications as cataract, glaucoma, diabetic retinopathy. Early detection of corneal endothelial dysfunction is important as it affects young patients *(Geloneck et al., 2015).*

The endothelium of cornea is a distinct layer of homogenously sized hexagonal cells. The quantity of these endothelial cells reduces by around 0.5%-0.6% (100-200 cells) each year *(Anbar et al., 2016).*

Several reviews have illustrated that the smallest alterations in the arrangement of the endothelial cells may evident in the distractions in the tautness of the endothelial blockade *(Joyce and Harris, 2010).*

As endothelial power of the cornea reduces, corneal hydration occurs so; the CCT increases *(Anbar et al., 2016).*

Corneal endothelial cell layer is sensible for sustaining the clarity of the cornea. There is restricted capacity of mitosis in corneal endothelium and once injured, residual cells expand to mask the lost region *(Benetz, 2011).*

Specular microscopy (SM) gives a non-invasive technique of morphological study of the corneal endothelium. The recent non-contact specular microscope to analysis corneal endothelium uses automated interfacing for gaining image via a discrete focusing technology *(McCarey et al., 2010).*

The present work aimed to evaluate corneal endothelial changes in type I diabetic patients and compare these changes to normal persons.

PATIENTS AND METHODS

This was a prospective comparative study for two groups:

Group A: thirty patients with type I DM with or without diabetic retinopathy.

Group B: thirty normal persons matched with age and sex.

It was carried out from 1st May 2019 to 30th April 2020 at Al- Azhar University Hospitals.

Excluded patients were that with history of ocular trauma, intraocular surgeries, ocular diseases (corneal dystrophies, glaucoma, and uveitis), contact lens wearers, any systemic diseases that could affect the eye rather than type I DM.

Ophthalmological examination included:

1. Uncorrected / best corrected visual acuity (UCVA/BCVA) expressed in LogMar scoring.

2. Refraction using automated refractometer (Topcon KR-800 Auto refractometer).
3. Intraocular pressure (IOP) measurement by Goldman Applanation tonometer.
4. Slit lamp biomicroscopy to assess corneal transparency, depth of anterior chamber, condition of pupil dilatation, lens morphology.
5. Slit lamp biomicroscopy using non-contact Volk 90 Diopter lens to assess state of diabetic retinopathy in dilated pupil fundus examination.
6. Non-contact specular microscope (Topcon sp-1p, Topcon Medical Inc., Japan) to assess the corneal endothelium.

Captured Images were analyzed by a built-in software where the corneal parameters were defined; ECD (cells/mm²), CV in cell size, HEX and CCC.

Statistical methods:

Data were accumulated, reviewed, coded and inserted to the Statistical Package for the Social Science (IBM SPSS) version 23. The quantifiable statistics were presented as mean, standard deviations and ranges. Qualitative variables were showed as figures and ratios. The associations relating the both groups respect to normally distributed numeric variables were done using the independent t-test. Non normal distributed numeric variables were compared by Mann-Whitney test. Spearman correlation coefficients were employed to evaluate the association involving both quantifiable parameters in the same group.

Receiver operating characteristic curve (ROC) was applied in the quantifiable method to define sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and Area under curve (AUC) of CCT and CD between Control and study groups. The confidence interval was put to 95% and the border of mistake agreed was determined to 5%. So, $P < 0.05$ was considered significant.

RESULTS

There was no statistically significant difference between normal group and diabetic patients as regard age and sex **(Table 1)**.

Table (1): A Comparison between Normal group and diabetic patients as regard age and sex

Parameters \ Groups		Normal group No. = 30	Patients group No. = 30	P-value
Age	Mean ± SD	33.00 ± 7.75	36.17 ± 8.70	0.142
	Range	19 – 47	19 – 51	
Sex	Female	15 (50.0%)	21 (70.0%)	0.114
	Male	15 (50.0%)	9 (30.0%)	

There was a statistically significant difference between normal group and diabetic patients as regard visual acuity but no statistically significant difference between two groups as regard IOP **(Table 1)**.

Table (2): A Comparison between Normal group and diabetic patients as regard age and sex

Parameters \ Groups	Normal group NO. = 60 eyes		Diabetic group NO. = 60 eyes		Mann-Whitney test
	Range	Median	Range	Median	P-value
Visual acuity in Log Mar	0 – 0.6	0.3	0 – 1.78	0.8	0.003
IOP	9 – 17	13	10 - 22	16	0.141

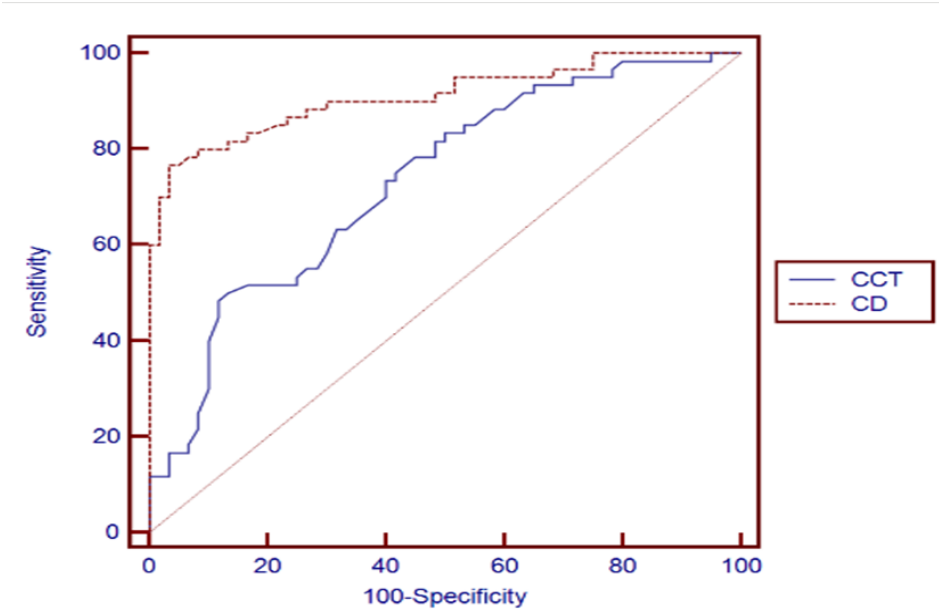

Figure (1): Sex distribution between studied groups

There was a statistically significant difference between normal group and patients group as regard CCT, CD, CV and HEX **(Table 3)**.

Table (3): A Comparison between Normal group and diabetic patients as regard CCT, CD, CV and HEX

Parameters \ Groups		Normal group	Patients group	P-value
		No. = 60	No. = 60	
CCT	Mean ± SD	513.82 ± 34.39	543.55 ± 31.96	0.001
	Range	440 – 584	457 – 611	
CD	Mean ± SD	3322.12 ± 189.50	2755.98 ± 378.59	0.001
	Range	2906 – 3686	2076 – 3498	
CV	Mean ± SD	25 ± 2.6	33.6 ± 4.3	0.001
	Range	20 – 32	24 – 43	
HEX	Mean ± SD	47.9 ± 3.7	37.1 ± 8.1	0.001
	Range	40 – 56	14 – 51	

ROC analysis for CCT. The best cut off point for CCT was > 545 with 0.50 sensitivity and 0.86 specificity. AUC was 0.733, with PPV =78.9 and NPV= 63.4 and the confidence interval was put to 95%. ROC analysis for CD. The best cut off point for CD was ≤ 3063 with 0.76 sensitivity and 0.96 specificity. AUC was 0.910 with PPV = 95.8 and NPV= 80.6 **(Figure 2)**.

ROC analysis was done for CV. The best cut off point for CV was > 29.5 with 0.83 sensitivity and 0.96 specificity. AUC was 0.96 with PPV = 96.2 and NPV= 85.27. ROC analysis was done for HEX. The best cut off point for HEX was > 45.5 with 0.75 sensitivity and 0.81 specificity. AUC was 0.88 with PPV = 80.4 and NPV= 76.6 **(Figure 3)**.

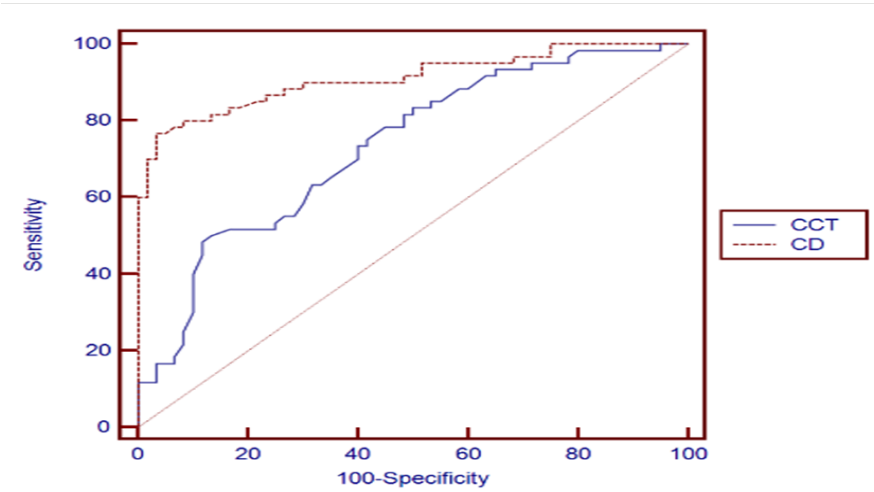

Figure (2): Receiver operating characteristic (ROC) curve of CCT and CD as a predictor between diabetic patients and control

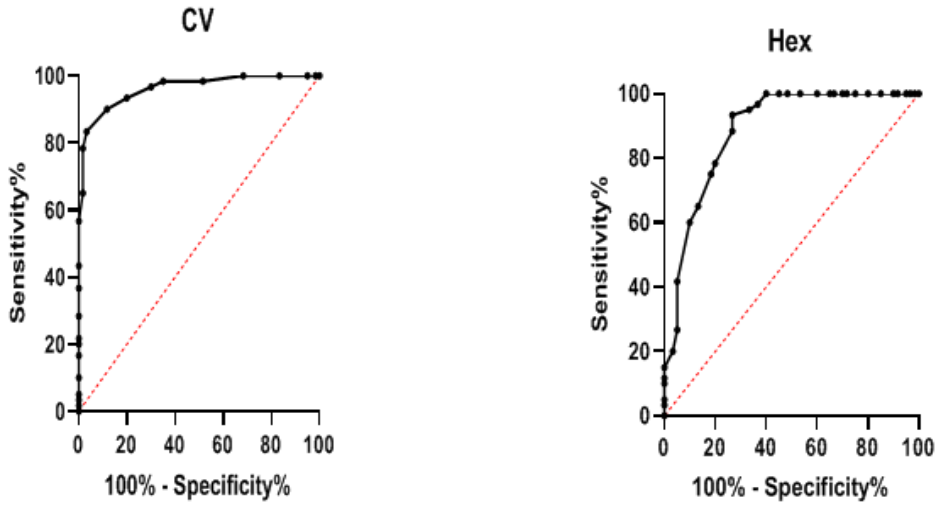

Figure (3): Receiver operating characteristic (ROC) curve of CV and HEX as a predictor between diabetic patients and control

There was a statistically significant difference between patients with DR and patients without DR as regard CCT **(Table 3)**.

Table (3): Comparison between patients with DR and patients without DR as regard specular parameters

Parameters \ Groups		No DR	DR	P-value
		No. = 40	No. = 20	
CCT	Mean ± SD	535.95 ± 30.93	558.75 ± 29.05	0.001<
	Range	457 – 606	524 – 611	
CD	Mean ± SD	2819.58 ± 373.34	2628.80 ± 365.28	0.065
	Range	2120 – 3498	2076 – 3100	
CV	Mean ± SD	33.9 ± 4.3	32.9 ± 4.42	0.403
	Range	26 – 43	24 – 42	
HEX	Mean ± SD	36.3 ± 8.34	38.50 ± 7.70	0.141
	Range	18 – 50	14 – 51	

There was a statistically significant positive correlation between CCT Vs. duration of DM and statistically significant positive correlation between CCT vs. IOP **(Table 4)**.

Table (4): Correlation of specular parameters (CCT, CD, CV and HEX) with other parameters (age, visual acuity, IOP and duration of DM)

Correlations	Mean ± SD	CCT		CD		CV		HEX	
	Range	R	P-value	R	P-value	R	P-value	R	P-value
Age	36.17 ± 8.70 (19 – 51)	0.286	0.126	-0.004	0.985	0.286	0.126	-0.004	0.985
Visual acuity	0.39 ± 0.38 (0 – 1.78)	0.195	0.136	-0.121	0.358	0.195	0.136	-0.121	0.358
IOP	13.30 ± 2.22 (10 – 22)	0.295*	0.022	-0.049	0.713	0.295*	0.022	-0.049	0.713
Duration of DM	11.87 ± 6.86 (2 – 30)	0.361**	0.005	-0.165	0.207	0.361**	0.005	-0.165	0.207

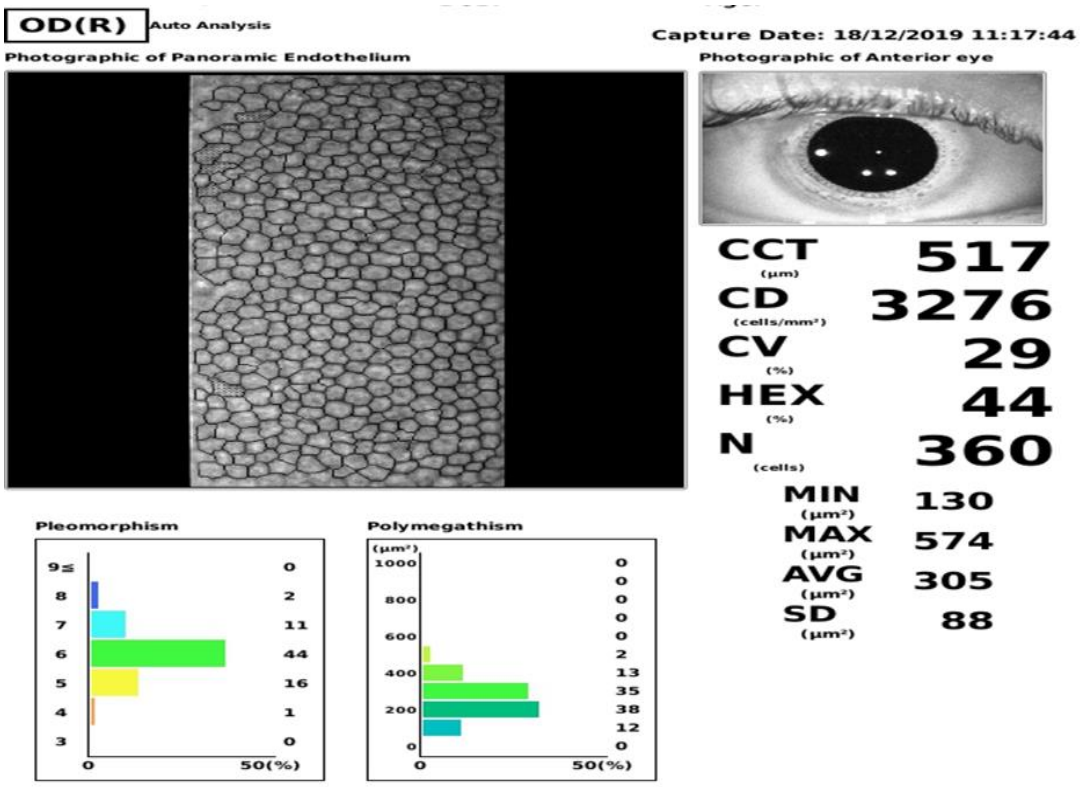

Figure (4): Specular photomicrograph of right eye to 22 years old type I diabetic male patient without retinopathy

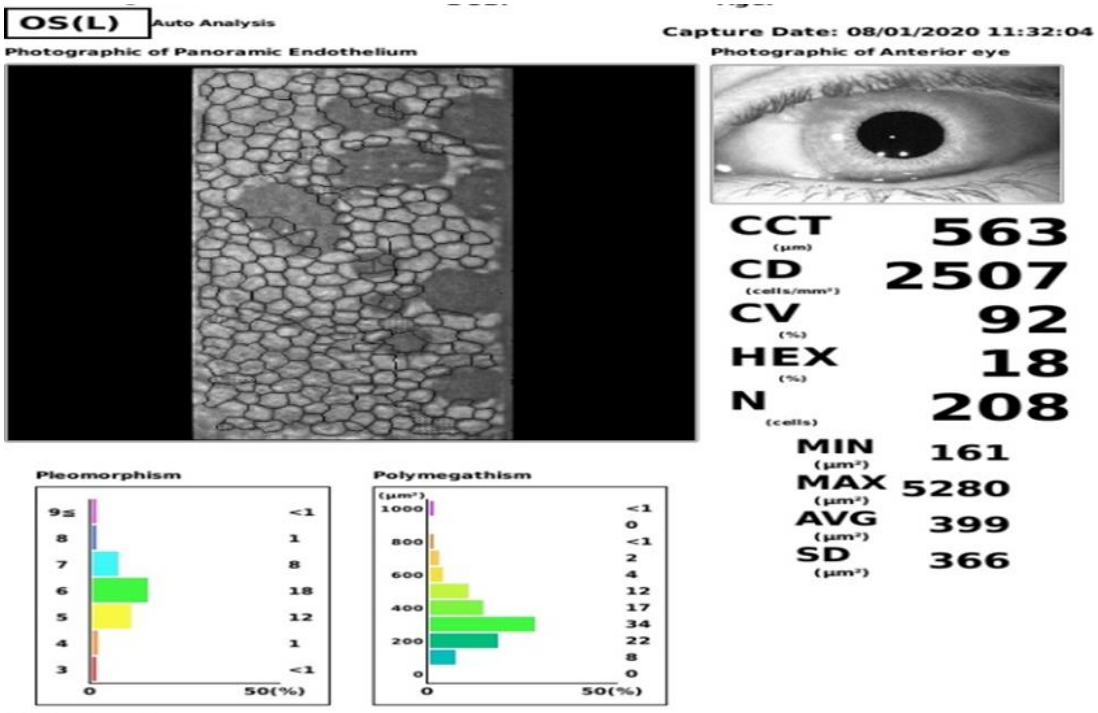

Figure (5): Specular photomicrograph of left eye to 40 years old type I diabetic female patient without retinopathy

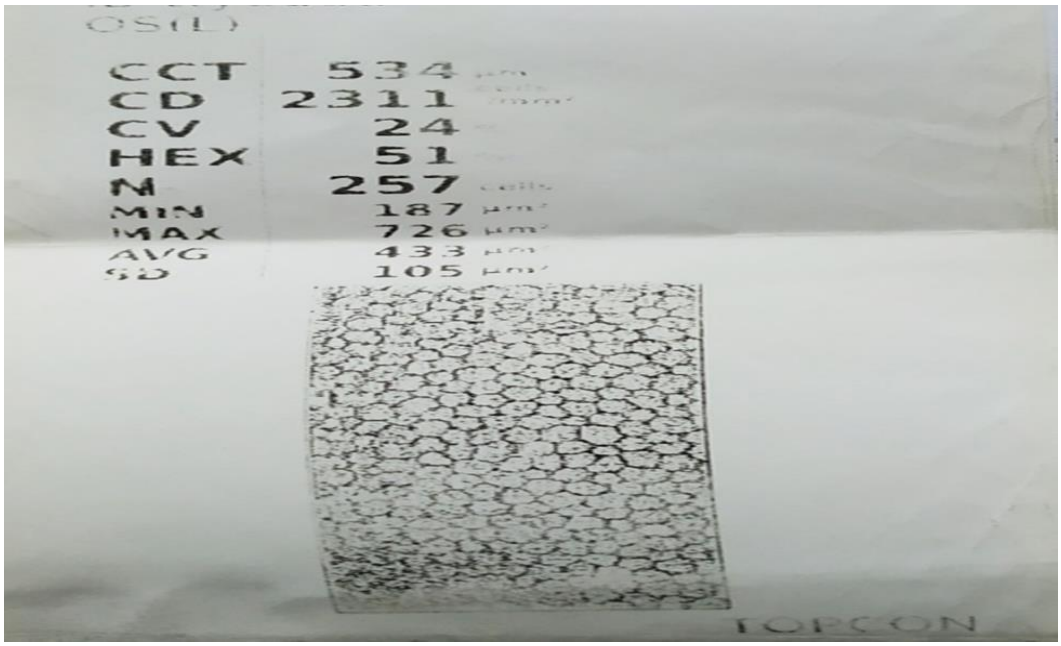

Figure (6): Specular microscopy of left eye to 32 years old type I diabetic male patient with diabetic retinopathy

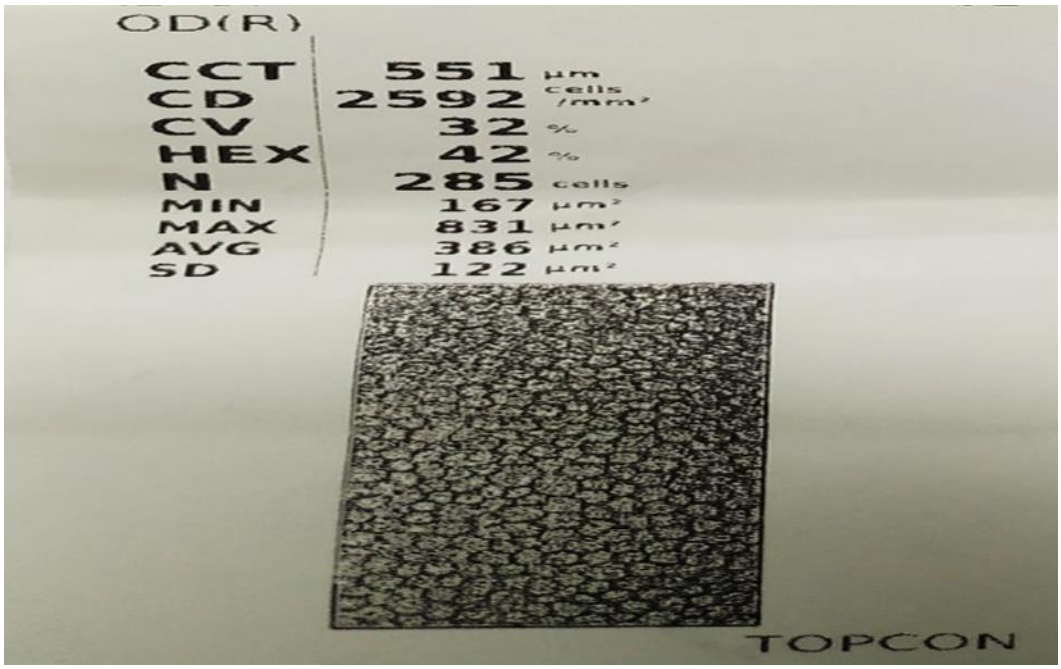

Figure (7): Specular microscopy of right eye to 24 years old type I diabetic female patient with diabetic retinopathy with retinopathy

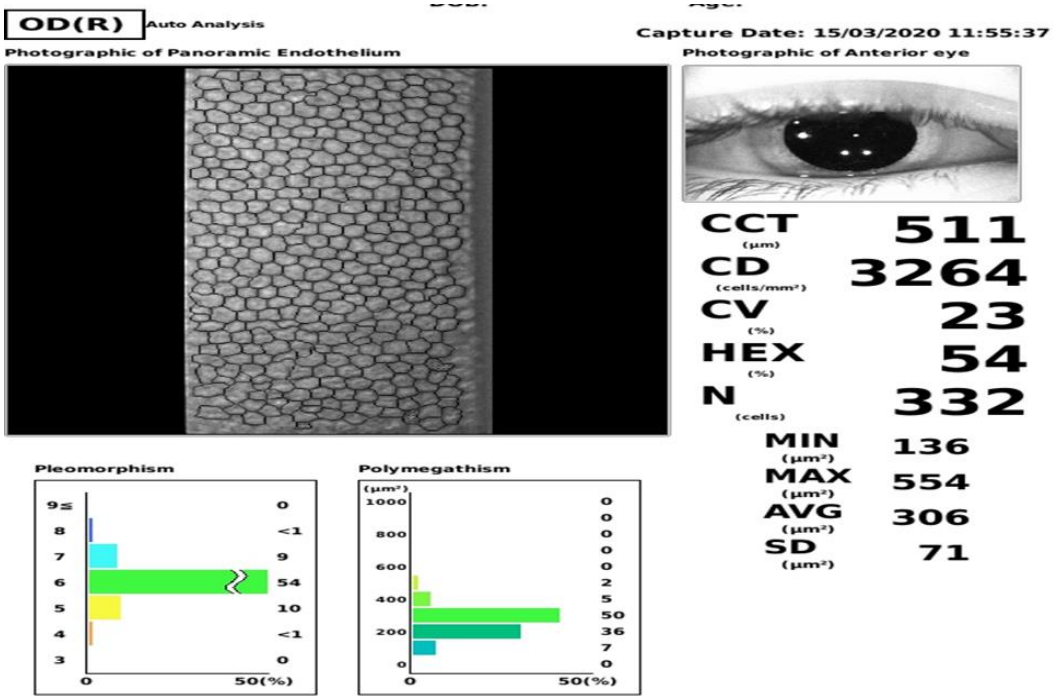

Figure (8): Specular photomicrograph of left eye to 30 years old normal male person

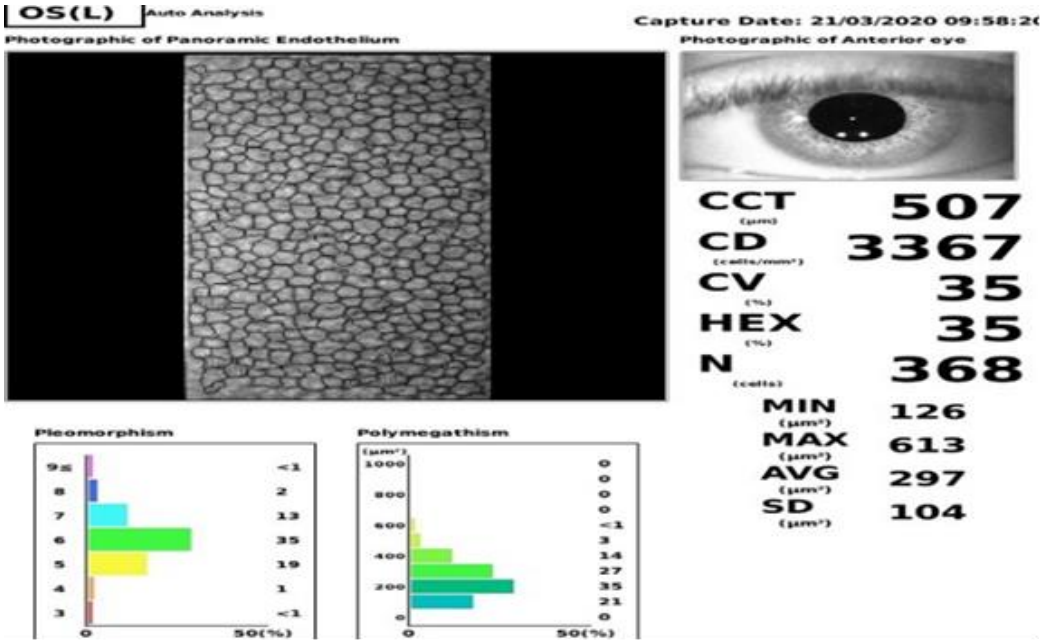

Figure (9): Specular photomicrograph of left eye to 29 years old normal female person

DISCUSSION

In the present study, there was a statistically significant decrease in endothelial cell density (ECD) and significant increase in central corneal thickness (CCT). Also, there was a statistically significant changes in coefficient of variation in cell size (CV)

and hexagonal cells percentage (HEX) as increase in CV (polymegathism) and decrease in hexagonality (pleomorphism) in type I diabetic patients compared to normal persons. The mean ECD in patients with type 1 diabetes was significantly lower than in the control group. Reduction of ECD in patients with type I diabetes was 20 % compared to normal persons, but in some normal persons ECD was lower than in some patients.

Several studies have been done to evaluate the corneal endothelial cells in type I diabetic patients. Most of these studies agreed that corneas in type I diabetic patients tend to be thicker and lower ECD and had more polymegathism and less hexagonality *(Anbar et al., 2016).*

In the present study, it was found that a statistically significant increase in CCT and decrease in ECD in patients with DR than patients without DR and a statistically significant positive correlation between CCT Vs. duration of DM. *Urban et al, (2013)* demonstrated a significant positive correlation between ECD and the duration of diabetes. *Gao et al, (2016)* confirmed that as the duration of diabetes extended, CCT increased while the corneal ECD decreased.

In the present study, CCT significantly increased in diabetic group compared to the normal group. *Tiutiuca (2013)* reported a significant increase in corneal thickness in diabetic children. *Urban et al., (2013)* demonstrated a significant increase in corneal thickness in diabetic children comparing to normal children. Possible explanations for increased corneal thickness in diabetic patients include (besides inhibition of the corneal endothelial pump) an increased endothelial permeability, which result from the metabolic effects of diabetes.

In the present study, CV significantly higher in diabetic group compared to normal persons and HEX was significantly lower in diabetic group compared to normal persons.

M`odis et al. (2010) found that Hb a1c was inversely correlated with ECD in type 1 diabetes, they demonstrated a significant decrease in ECD in type I diabetics compared with normal subjects, increased corneal thickness, also they recorded significant correlation between the endothelial morphology and grade of diabetic retinopathy, while in type 2 diabetes no changes occurred.

Diabetic patients developed corneal endothelial cell polymegathism while still retaining normal cell density for their age *(Sudhir et al., 2012).* The research done by *Mathew et al (2011)* had shown that the removal of cataract is exceptionally traumatizing for the endothelium in eyes of diabetic patients. The diabetic endothelium was found to be under greater metabolic stress and had less functional reserve after manual small incision cataract surgery.

Evaluating the condition of the corneal endothelium is important since one of the most frequent reasons of corneal endothelium cells damage is cataract surgery, and cataract is one of the most common ophthalmic complications of diabetes *(Urban et a, 2013).*

CONCLUSION

The consequences of the study may reinforce that the cornea in patients with type 1 DM had a reduction in endothelial

cell density and increase in central corneal thickness also with significant changes in CV and HEX as increase in CV and decrease in HEX.

Duration of diabetes is the reason that changes CCT and noticed alterations could prompt to corneal decompensating and dysfunction due to decrease of ECD in the future. Also diabetic retinopathy is a factor that affects CCT.

The Study recommends specular microscopy of the corneal endothelium for type I diabetic patients before any intra ocular surgery to avoid the risk of corneal decompensating.

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دراسة الخلايا المبطنة للقرنية في مرضى البول السكري من النوع الأول والأشخاص الأصحاء بإستخدام جهاز المجهر البراق

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خلفيـــة البحـــث: داء البـــول الســـكري هـــو اضـــطراب عـــام يغيـــر عمليـــات التمثيـــل الغـــذائي الرئيســـية التـــى تـــزعج وظـــائف الأجهـــزة فـــى الجســـم. داء الســـكرى مـــن النـــوع الأول هـــو اضـــطراب النمثيـــل الغـــذائي الشـــائع بشـــكل عـــام فـــى مرحلـــة البلـــوغ. يعـــاني واحـــد مـــن كـــل ٤٠٠-٦٠٠ مـــن الأحـــداث والبـــالغين مـــن مـــرض السكرى من النوع الأول. وقد ارتفع معدل حدوثه خلال السنوات الجديدة.

الهـــدف مـــن البحـــث: مقارنـــة خلايـــا بطانـــة القرنيـــة لمرضـــي البـــول الســـكري مـــن النـــوع الأول وذلـــك بإســـتخدام جهـــاز المجهـــر البـــراق بأشـــخاص أصـــحاء متـــوافقين فـــى العمـــر والجـــنس وذلـــك مـــن حيـــث كثافـــة خلايـــا بطانـــة القرنيـــة، معامـــل التبـــاين فـــى حجـــم الخلايـــا، التغييرفـــى نســـبة الخلايـــا ذات الشـــكل السداســـي، ســـمك القرنيـــة المركزى.

المرضـــى وطـــرق البحـــث: اشـــتملت الدراســـة علـــى مجمـــوعتين: مجموعـــة (أ) ثلاثـــون مريضـــا بمـــرض البـــول الســـكري مـــن النـــوع الأول ســـواء مـــع وجـــود إعـــتلال الشـــبكيه الســـكري مـــن عـــدم وجـــوده، ومجموعـــة (ب) ثلاثـــون شخصـــا طبيعيـــا. بعـــد اختيـــار المرضـــي المصـــابون بمـــرض البـــول الســـكري مـــن النـــوع الأول وبعـــد تطبيـــق معـــايير الإســـتبعاد مـــن الدراســـة وبعـــد أن تـــم شـــرح إجـــراءات الدراســـة تـــم الآتـــى: (أ) أخـــذ التـــاريخ المرضـــي للحـــالات. (ب) الفحـــص مـــن حيـــث: ١- قيـــاس حـــدة الإبصـــار ٢- قيـــاس إنكســـار العـــين ٣- قيـــاس ضـــغط العـــين ٤- فحـــص قـــاع العـــين ٥- الفحـــص المجهـــرى البـــراق لخلايـــا بطانـــة القرنيـــة. أجريـــت

الدراسة في مستشفيات جامعة الأزهر بالقاهرة فى الفترة ما بين مايو ٢٠١٩ إلى أبريل ٢٠٢٠.

النتائج: هناك نقص فى كثافة الخلايا سداسية الشكل المبطنة للقرنية بنسبة ٧٦% فى مرضى البول السكري من النوع الأول مقارنة بالأشخاص الطبيعيين، وأيضا زيادة فى سمك القرنية المركزي فى مرضي البول السكري من النوع الأول مقارنة بالأشخاص الطبيعين، وايضا زيادة معامل التباين فى الخلايا ونقص فى نسبة الشكل السداسي للخلايا.

الاستنتاج: القرنية فى مرضى البول السكري من النوع الأول تعاني من نقص كثافة الخلايا المبطنة للقرنية وزيادة سمك القرنية المركزى، كما يوجد تغيرات فى معامل التباين فى الخلايا ونسبة الشكل السداسي وجد زيادة فى معامل التباين فى الخلايا ونقص فى نسبة الشكل السداسي للخلايا، ومدة مرض السكر هو العامل فى تغير سمك القرنية المركزي وكذلك وجود اعتلال الشبكيه السكري، كل هذه التغيرات تؤدي الى نقص كفاءة القرنية واعتلال وظيفتها بسبب نقص كثافة الخلايا المبطنة للقرنية مستقبلا.

الكلمات الدالة: جهاز المجهر البراق، كثافة خلايا بطانة القرنية، معامل التباين فى حجم الخلايا، نسبة الخلايا ذات الشكل السداسي، سمك القرنية المركزى.