






# Corneal Endothelial Morphological Alterations in Type 2 Diabetes: Associations with Glycemic Control, Disease Duration, and Diabetic Retinopathy Severity—A Cross-Sectional Study in Benghazi, Libya

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## Abstract

**Background** The corneal endothelium is essential for maintaining corneal transparency and fluid regulation, and its dysfunction can lead to corneal edema and decreased visual acuity. Corneal specular microscopy is used to detect corneal disorders early.

**Aim** This study aimed to evaluate morphological changes in the corneal endothelium of patients with type 2 diabetes mellitus (DM) using specular microscopy.

**Methods** This study enrolled 50 individuals with type 2 diabetes and 50 nondiabetic individuals as control subjects. Patients with certain ocular and systemic conditions were excluded. The collected data included demographic information, medical history, recent hemoglobin A1c (HbA1c) values, visual acuity, ophthalmological examination, and diabetic retinopathy (DR) staging. The corneal endothelial morphology was evaluated using a noncontact specular microscope, which measured corneal endothelial cell density (ECD), central corneal thickness (CCT), coefficient of variation of cell size (CV), and hexagonality. The data were analyzed using SPSS software, and the results were presented as mean  $\pm$  standard deviation, numbers, and percentages. An unpaired *t*-test was used to compare different means, and a *p*-value less than 0.05 was considered statistically significant.

**Results** A majority of diabetic patients (62%) had diabetes for more than 10 years, and 58% of them had higher than 7.5% HbA1c levels. In terms of DR severity, 46% of patients had mild nonproliferative diabetic retinopathy (NPDR), 36% had moderate NPDR, and 10% had severe NPDR. There were significant differences between diabetic and nondiabetic groups in corneal ECD ( $2480 \pm 223$  cells/mm<sup>2</sup> for DM group vs.  $2652 \pm 234$  cells/mm<sup>2</sup> for non-DM), hexagonality ( $39.6 \pm 2.8\%$  for DM group vs.  $47 \pm 2.1\%$  for non-DM), CV ( $42 \pm 2.9\%$  for DM group vs.  $35.5 \pm 2.3\%$  for non-DM), and CCT ( $550 \pm 14.8$   $\mu$ m for DM group vs.  $530 \pm 9.6$   $\mu$ m for non-DM). Patients who had

## Keywords

- ▶ corneal endothelial morphology
- ▶ type 2 diabetes mellitus
- ▶ diabetic retinopathy
- ▶ specular microscopy
- ▶ Benghazi
- ▶ Libya

diabetes for more than 10 years had significantly lower ECD ( $2356 \text{ cells/mm}^2$  vs.  $2689 \text{ cells/mm}^2$ ), lower hexagonality (39 vs. 41%), and higher CV (43 vs. 41%) and higher CCT ( $553.9 \pm 4.6$  vs.  $545.5 \pm 4.0$ ) than those with less than 10 years of diabetes. As the severity of DR increased, there was a significant decrease in ECD (from  $2641 \pm 194 \text{ cells/mm}^2$  for mild NPDR to  $2310 \pm 82 \text{ cells/mm}^2$  for severe PDR), a decrease in hexagonality (from  $40.9 \pm 3.2\%$  for mild PDR to  $37.4 \pm 1.1\%$  for severe PDR), an increase in CV (from  $40.1 \pm 2.3\%$  for mild PDR to  $44 \pm 2.9\%$  for severe PDR), and an increase in CCT (from  $543.7 \pm 13.8$  for mild PDR to  $563.8 \pm 2.9$  for severe PDR).

**Conclusion** This study revealed that type 2 diabetes is associated with significant reductions in ECD and hexagonality, as well as an increase in CV and CCT. The severity of DR and the duration of diabetes were correlated with changes in these parameters. These findings underscore the need for a comprehensive evaluation of corneal health in diabetic patients.

#### ملخص المقال باللغة العربية

التغيرات المورفولوجية لبطانة القرنية في مرض السكري من النوع 2: العلاقة مع التحكم في نسبة السكر في الدم، ومدة المرض، وشدة اعتلال الشبكية السكري. دراسة مقطعية في بنغازي، ليبيا.

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**خلفية:** تعتبر بطانة القرنية ضرورية للحفاظ على شفافية القرنية وتنظيم سائلها، ويمكن أن يؤدي خللها إلى وذمة القرنية وانخفاض حدة البصر. يستخدم الفحص المجهرى للقرنية للكشف عن اضطرابات القرنية في وقت مبكر.

**الهدف:** هدفت هذه الدراسة إلى تقييم التغيرات المورفولوجية في بطانة القرنية للمرضى الذين يعانون من داء السكري من النوع 2 باستخدام المجهر المرأوي.

**الطرق:** شملت الدراسة 50 فردًا مصابين بداء السكري من النوع 2 و50 فردًا غير مصابين بالسكري كمجموعة تحكم مرجعية. تم استبعاد المرضى الذين يعانون من الأمراض العينية والجهازية الأخرى. تضمنت البيانات التي تم جمعها المعلومات الديموغرافية، والتاريخ الطبي، وقيم الهيموجلوبين السكري HbA1c الحديثة، وحدة البصر، وفحص العيون، ومراحل اعتلال الشبكية السكري. تم تقييم مورفولوجيا بطانة القرنية باستخدام المجهر المرأوي، والذي يقيس كثافة خلايا بطانة القرنية (ECD)، وسمك القرنية المركزي (CCT)، ومعامل الاختلاف في حجم الخلية (CV)، والسداسية. تم تحليل البيانات باستخدام برنامج SPSS وتم عرض النتائج على شكل متوسط  $\pm$  الانحراف المعياري والنسب المئوية. تم استخدام اختبار t غير المقترن لمقارنة الاختلاف الإحصائي بين مجموعتين، واعتبرت قيمة P أقل من 0.05 ذات دلالة إحصائية.

**النتائج:** يعاني غالبية المرضى (62%) من مرض السكري لأكثر من 10 سنوات، وكان لدى 58% منهم مستويات الهيموجلوبين السكري أعلى من 7.5%. من حيث شدة اعتلال الشبكية السكري، كان 46% من المرضى يعانون من اعتلال الشبكية السكري غير الكاثري الخفيف، و36% لديهم اعتلال متوسط، و10% لديهم اعتلال شديد. كانت هناك فروق ذات دلالة إحصائية بين المجموعة المصابة بالسكري والمجموعة غير المصابة في كثافة الخلايا بطانة القرنية ( $223 \pm 2480$  خلية/م<sup>2</sup> لمجموعة المرضى السكري مقابل  $234 \pm 2652$  خلية/م<sup>2</sup> لغير مرضي السكري)، والسداسية ( $2.8 \pm 39.6$  لمجموعة المرضى السكري مقابل  $2.1 \pm 47$  % لغير مرضي السكري)، واختلاف في حجم الخلية ( $2.9 \pm 42$  / لمجموعة المرضى السكري مقابل  $2.3 \pm 35.5$  / لغير مرضي السكري). كما كان هناك اختلاف في سمك القرنية المركزي ( $14 \pm 550$  مايكرومتر لمجموعة المرضى السكري مقابل  $9.6 \pm 530$  مايكرومتر لغير مرضي السكري).

كان لدى المرضى الذين يعانون من مرض السكري لأكثر من 10 سنوات انخفاض ملحوظ في كثافة الخلايا البطانة ( $2356$  خلية/ملم<sup>2</sup> مقابل  $2689$  خلية/ملم<sup>2</sup>)، وانخفاض السداسية ( $39$  / مقابل  $41$ )، وتباين أعلى في حجم الخلية ( $43$  / مقابل  $41$ ). وسمك القرنية المركزية ( $553.9 \pm 4.6$  مقابل  $545.5 \pm 4.0$ ) مقارنة بالمرضى لأقل من 10 سنوات، كما أن زيادة شدة اعتلال الشبكية السكري كان مصحوبا بانخفاض كبير في كثافة الخلايا البطانة ( $2641 \pm 194$  خلية / م<sup>2</sup> لاعتلال الشبكية السكري الخفيف إلى  $2310 \pm 82$  خلية / م<sup>2</sup> لاعتلال الشبكية السكري الشديد)، وانخفاض في السداسية (من  $40.9 \pm 3.2$  % لاعتلال الشبكية السكري الخفيف إلى  $37.4 \pm 1.1$  % لاعتلال الشبكية السكري الشديد)، وزيادة في تباين حجم الخلية (من  $40.1 \pm 2.3$  % لاعتلال الشبكية السكري الخفيف إلى  $44 \pm 2.9$  % لاعتلال الشبكية السكري الشديد) وزيادة في سمك القرنية المركزي ( $543.7 \pm 13.8$  لاعتلال الشبكية السكري الخفيف إلى  $563.8 \pm 2.9$  لاعتلال الشبكية السكري الشديد).

**الغائمة:** كشفت الدراسة أن مرض السكري من النوع الثاني يرتبط بانخفاض كبير في كثافة الخلايا البطانة والشكل السداسي للشبكية، بالإضافة إلى زيادة في التباين في حجم الخلية وسمك القرنية المركزي. ترتبط شدة اعتلال الشبكية السكري ومدة الإصابة بمرض السكري بالتغيرات في هذه المعلمات. تؤكد هذه النتائج الحاجة إلى إجراء تقييم شامل لصحة القرنية لدى مرضى السكري.

**الكلمات المفتاحية:** مورفولوجيا بطانة القرنية، داء السكري من النوع الثاني، اعتلال الشبكية السكري، الفحص المجهرى، بنغازي، ليبيا.

## Introduction

The corneal endothelium plays a crucial role in maintaining the clarity of the cornea by constantly pumping water to keep it in a relatively dehydrated state.<sup>1,2</sup> Cellular size and shape are correlated with pump function, with increased size (polymegethism) and shape variation (pleomorphism) correlated with reduced capacity for dehydration.<sup>3</sup> Eyes exhibiting an endothelial cell count below 500 cells per mm<sup>2</sup> are susceptible to the development of corneal edema.<sup>4</sup> Corneal specular microscopy is used for assessing corneal endothelial health that aids in diagnosis, treatment, and surgical planning.<sup>5,6</sup> It analyzes cell size, shape, and population, detecting early dysfunction.<sup>7,8</sup> In addition, corneal specular microscopy is utilized in scientific investigations to examine the various factors that may influence endothelial cells.<sup>9-11</sup>

Type 2 diabetes mellitus (T2DM) is a chronic metabolic condition characterized by increased levels of blood glucose that result from both insulin resistance and deficiency.<sup>12</sup> Globally, the prevalence of individuals affected by this condition is on a trajectory of significant growth and is expected to continue increasing substantially in the coming decades with higher rates in low- and middle-income countries.<sup>13</sup> T2DM involves a complicated interaction of several mechanisms, such as oxidative stress, inflammatory responses, and impaired mitochondrial activity; these inter-related processes ultimately contribute to the dysfunction of the cells.<sup>14</sup> Diabetes causes vision-impairing ocular complications such as diabetic retinopathy (DR), glaucoma, cataracts, and keratopathy.<sup>15</sup> Additionally, it also affects corneal endothelial cells, thickness, and sensitivity, due to vascular and neuropathy complications. Diabetic keratopathy exhibits a significant incidence in individuals with diabetes, affecting around 50% of diagnosed cases.<sup>16</sup> The end-products of advanced glycation may accelerate ocular endothelial cell damage from oxidative stress and inflammation.<sup>17</sup> Diabetes-induced endothelial dysfunction results in corneal complications such as edema, bullous keratopathy, and cell loss, necessitating possible corneal transplants.<sup>18</sup> Several studies have indicated that individuals with DM have elevated central corneal thickness (CCT) values when compared to individuals without the condition.<sup>19</sup> Previous studies have identified a relationship between CCT and the duration of DM.<sup>20</sup> Others did not establish a significant association between DM duration, glycated hemoglobin A1c (HbA1c) levels, and CCT.<sup>21</sup> A recent study indicated a higher coefficient of variation (CV) and reduced cell hexagonality in patients with type I and II DM, but found no differences in endothelial cell density (ECD).<sup>22</sup> A few studies have been undertaken to examine the association between alterations in corneal endothelial parameters and the various stages of DR. Although some studies did not observe significant changes in these variables in relation to the stages of DR or the duration of DM,<sup>23</sup> other studies have demonstrated significant correlations between corneal parameters, duration of DM, and severity of DR.<sup>24,25</sup> It is essential to thoroughly evaluate corneal health, especially when planning surgical interventions such as cataract surgery. Therefore,

preoperative corneal evaluation may be necessary, especially in the Libyan population, where the prevalence of DM has been increasing in recent years, with estimates ranging from 7.2 to 15.3%.<sup>26</sup>

## Aim of the Study

The aim of this research is to evaluate the morphological alteration in the corneal endothelium parameters of patients with T2DM using a corneal specular microscope. This study seeks to determine the impact of diabetes duration, glycemic control (HbA1c levels), and DR severity on the corneal endothelium.

## Methods

This is an observational case-control study conducted at Benghazi Teaching Eye Hospital, from January 2023 to June 2023. This study included 50 patients (30 males and 20 females, totaling 50 eyes) with T2DM and 50 control subjects (nondiabetics) (50 eyes, 25 males and 25 females).

## Inclusion Criteria

Patients of both genders aged 50 years or older diagnosed with T2DM were examined. T2DM diagnosis was confirmed by the endocrinology department at the Benghazi Diabetes Diagnostic and Treatment Center. The control group consisted of patients aged 50 years or older without diabetes.

## Exclusion Criteria

This study excluded individuals who had current or past eye infections or inflammations, as well as those with conditions that affect tear production. People who used certain eye drops or medications that can disrupt tear production were also excluded, along with those who had previous ocular surgery, trauma, laser treatment, or underlying corneal diseases like keratoconus. Additionally, people with glaucoma, pterygium, lid diseases, or who wore contact lenses were not included. Individuals who were unable to provide informed consent were also excluded from this study.

## Data Collection

Data collected included demographic parameters (age, sex, and medical history), diabetes duration, most recent HbA1c value, clinical features (visual acuity and comprehensive ophthalmic examination, including slit-lamp biomicroscope and fundus examination), and pupillary dilation using tropicamide eye drops and a noncontact lens (+90 D). Intraocular pressure was measured using compressed air. Based on fundus examination findings and following the Early Treatment Diabetic Retinopathy Study Criteria, patients with DR were categorized into four groups: mild nonproliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, and PDR. A noncontact specular microscope (SP-1P Topcon) was used to evaluate corneal endothelial cell count, cell density, CV of cell size, and hexagonality. All measurements were taken by the researcher at the Benghazi Eye Hospital. The computer software automatically evaluated, calculated, and displayed the mean cell density (cells/mm<sup>2</sup>),

CV in cell size, and percentage of hexagonal cells. The CV% was used as an index of cell size variation (polymegethism), while the hexagonality was used as an index of cell shape variation (pleomorphism). The mean of each variable from the three best images of the central cornea was used for studying ECD, CV, and hexagonality. CCT was obtained for all subjects using Topcon Aladdin at the same time.

### Ethical Considerations

This study received approval from the Ethics Research Committee of Benghazi Teaching Eye Hospital and adhered to the principles of the Declaration of Helsinki. Before being included in this study written consent was obtained from all participants. Each patient has explained the nature of this study, its purpose, procedures, duration, potential risks, and benefits involved, as well as any discomfort it might cause. Each patient was informed that participation was voluntary, they could withdraw from this study at any time without giving explanations, and their decision to withdraw would not affect their medical treatment or their relationship with the treating physician.

### Statistical Analysis

Data from this study were analyzed using SPSS version 23 software for Windows. Descriptive statistics were used to express the results as mean  $\pm$  standard deviation, numbers, and percentages. An unpaired *t*-test was used to calculate the significance of differences between two groups. A *p*-value less than 0.05 was determined to be statistically significant.

### Results

The diabetic group's age range was 50 to 86 years, with a mean age of  $65.86 \pm 10.9$  years, while the control group's age range was 50 to 81 years, with a mean age of  $63.6 \pm 10.4$  years. The mean duration of diabetes was  $14.88 \pm 7.44$  years, with 38% of patients having a diabetes duration for less than 10 years and 62% of patients having a duration of more than 10 years. The mean HbA1c level was  $7.8 \pm 0.88\%$ , with 42% of patients having an HbA1c level less than 7.5% and 58% of patients having a level higher than 7.5%. Regarding the DR status, 46% of patients had mild NPDR, 36% had moderate NPDR, 10% had severe NPDR, and 8% had PDR (see ► **Table 1**).

► **Table 2** presents the effects of T2DM on endothelium parameters. The diabetic group had significantly lower ECD ( $2480.7 \pm 223.6$  vs.  $2652.3 \pm 234.2$ ) and hexagonality

**Table 1** Details of the duration of DM, HbA1c, and DR status in the DM group

Variable	DM group, n (%)
Mean duration (years) $\pm$ SD	$14.88 \pm 7.44$
$\leq 10$ years	19 (38%)
$> 10$ years	31 (62%)
HbA1c in (%) mean $\pm$ SD	$7.8 \pm 0.88$
$\leq 7.5$	21 (42%)
$> 7.5$	29 (58%)
DR status (n, %)	
No DR	0
Mild NPDR	23 (46%)
Moderate NPDR	18 (36%)
Severe NPDR	5 (10%)
PDR	4 (8%)

Abbreviations: HbA1c, hemoglobin A1c; DM, diabetes mellitus; DR, diabetic retinopathy; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; SD, standard deviation.

( $39.6 \pm 2.8$  vs.  $47.04 \pm 2.1$ ) compared to the nondiabetic group. Conversely, CV in cell size and CCT were significantly higher in the diabetic group ( $42 \pm 2.9$  vs.  $35.5 \pm 2.3$ ) and ( $550.5 \pm 14.8$  vs.  $530.4 \pm 9.6$ ), respectively.

► **Table 3** shows the impact of the three variables studied on the endothelium parameters of patients with T2DM. Specifically, individuals who had DM for more than 10 years when compared to those who had DM for less than 10 years had statistically significantly lower values for both ECD ( $2360 \pm 56.7$  vs.  $2685 \pm 65.5$ ) and hexagonality ( $38.9 \pm 0.7$  vs.  $40.8 \pm 1.3$ ), but higher values for CCT ( $553.9 \pm 4.6$  vs.  $545.5 \pm 4.0$ ) and CV% ( $43.1 \pm 0.73$  vs.  $40.8 \pm 0.8$ ). Similar patterns were seen with HbA1c levels, where patients with HbA1c levels more than 7.5% had statistically significantly lower values for both ECD ( $2383 \pm 75$  vs.  $2561 \pm 87$ ) and hexagonality ( $38.9 \pm 0.7$  vs.  $40.8 \pm 1.0$ ), but higher values for CCT ( $553.9 \pm 4.7$  vs.  $545.8 \pm 2.6$ ) and CV% ( $43.1 \pm 0.73$  vs.  $40.8 \pm 0.8$ ), when compared to those with HbA1c levels less than 7.5%. The severity of DR has a similar impact, where increasing severity of PDR had resulted in a gradual decrease in ECD (from  $2641 \pm 194.8$  to  $2310 \pm 82.4$ ) and hexagonality (from  $40.9 \pm 3.2$  to  $37.4 \pm 1.1$ ) and an increase in CV (from  $40.1 \pm 2.3$  to  $44 \pm 2.9$ ) and CCT (from  $543.7 \pm 13.8$  to  $563.8 \pm 2.9$ ).

**Table 2** Comparison of endothelium parameters in DM versus non-DM groups

Endothelium parameters (mean $\pm$ SD)	DM group	Non-DM group	<i>p</i> -Value <sup>a</sup>
ECD (cells/mm <sup>2</sup> )	$2480.7 \pm 223.6$	$2652.3 \pm 234.2$	$<0.001$
CV in cell size (%)	$42 \pm 2.9$	$35.5 \pm 2.3$	$<0.001$
Hexagonality (%)	$39.6 \pm 2.8$	$47.04 \pm 2.1$	$<0.001$
CCT ( $\mu$ m)	$550.5 \pm 14.8$	$530.4 \pm 9.6$	$<0.001$

Abbreviations: CCT, central corneal thickness; CV, coefficient of variation; DM, diabetes mellitus; ECD, endothelial cell density; SD, standard deviation.

<sup>a</sup>Statistically significant using unpaired *t*-test.

**Table 3** Associations of glycemic control, disease duration, and diabetic retinopathy severity with endothelium parameters

Variable		ECD (cells/mm <sup>2</sup> )	CV (%)	CCT (μm)	Hexagonality (%)
Duration (years)	≤ 10 years n = 19	2685 ± 65.5	40.8 ± 0.8	545.5 ± 4.0	40.8 ± 1.3
	> 10 years n = 31	2360 ± 56.7 <sup>a</sup>	43.1 ± 0.73 <sup>a</sup>	553.9 ± 4.6 <sup>a</sup>	38.9 ± 0.7 <sup>a</sup>
HbA1c	≤ 7.5% n = 21	2561 ± 87	40.85 ± 0.79	545.8 ± 2.64	40 ± 1.05
	> 7.5 n = 29	2383.5 ± 75 <sup>a</sup>	43 ± 0.99 <sup>a</sup>	553.9 ± 4.7 <sup>a</sup>	38.9 ± 0.74 <sup>a</sup>
DR status	Mild NPDR (n = 23)	2641 ± 194.8	40.1 ± 2.3	543.7 ± 13.8	40.9 ± 3.2
	Moderate NPDR (n = 18)	2382.8 ± 150.4 <sup>b</sup>	43 ± 2.2 <sup>b</sup>	549.9 ± 11.1 <sup>b</sup>	39.2 ± 1.4 <sup>b</sup>
	Severe NPDR (n = 5)	2310 ± 82.4 <sup>b</sup>	44 ± 2.9 <sup>b</sup>	563.8 ± 2.9 <sup>b</sup>	37.4 ± 1.1 <sup>b</sup>
	PDR n = 4	2211 ± 41.1 <sup>b</sup>	46.2 ± 1.2 <sup>b</sup>	575.2 ± 2.8 <sup>b</sup>	36.2 ± 0.9 <sup>b</sup>

Abbreviations: CCT, central corneal thickness; CV, coefficient of variation; ECD, endothelial cell density; DR, diabetic retinopathy; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

<sup>a</sup>Statistically significant using unpaired t-test from the corresponding group.

<sup>b</sup>Statistically significant using unpaired t-test from mild NPDR group.

## Discussion

T2DM can cause several metabolic and physiological abnormalities in different parts of the body, including the retina. The endothelial cells lining the blood vessels in the eye can be affected by T2DM, which can result in changes in various parameters such as CCT, ECD, and corneal hexagonality. These changes can ultimately impact vision and increase the risk of developing eye diseases such as glaucoma and DR.

This study aimed to investigate the impact of T2DM on various corneal endothelial parameters in Benghazi, Libya, using specular microscopy. The findings of this study indicate a significant (6.47%) reduction in the mean ECD among diabetic patients compared to healthy individuals. The diabetic group also showed a notable decrease in hexagonality percentage and an increase in polymegathism (CV) compared to the healthy group. Similar findings of reductions in ECD and increases in CV% among diabetic patients compared to healthy controls were reported.<sup>23,27</sup> However, other studies<sup>28,29</sup> reported no significant differences in ECD, Hexagonality (HEX), or CV between diabetic and nondiabetic groups. On the other hand, another report<sup>30</sup> found a significantly reduced ECD in diabetes patients compared to healthy controls, but no significant difference in CV or hexagonality between the two groups.

Our study also found a significant increase in CCT in the diabetic group compared to the healthy control group. These results are consistent with other results<sup>31,32</sup> who also observed a significant increase in CCT in diabetic patients compared to healthy controls but did not observe a significant difference in ECD between the two groups.

When we looked for the factors that will affect corneal endothelial parameters in our patients, we found that pro-

longed duration of DM (>10 years) and poor glycemic control (HbA1c > 7.5%) was associated with a significant reduction in ECD and hexagonality compared to those with a duration of less than 10 years and HbA1c less than 7.5%. On the other hand, there was a significant increase in the CV in cell size and CCT among patients who had a disease duration of more than 10 years and HbA1c more than 7.5%. Similar results were reported by Jha et al<sup>27</sup> that increasing duration and poor glycemic control showed a significant reduction in ECD and hexagonality, and an increase in CCT and CV. However, Choo et al<sup>21</sup> and El-Agamy et al<sup>23</sup> did not find significant changes in the cornea associated with an increase in the duration of DM or high HbA1c levels. Altay et al<sup>33</sup> documented significantly higher CCT in hyperglycemic groups without significant changes in other parameters.

Regarding the comparison of mean values of CCT, ECD, CV, and hexagonality among the four diabetic groups based on their DR status, our study indicates that as the severity of DR increased from mild NPDR to PDR, there was a significant gradual decrease in ECD, hexagonality, and a significant increase in CV and CCT, indicating a strong association between DR and corneal endothelial parameters changes. Similar findings were reported by Jha et al,<sup>27</sup> while El-Agamy et al<sup>23</sup> and Sudhir et al<sup>34</sup> did not find significant differences between eyes with and without DR. A study conducted by Durukan<sup>35</sup> reported that there was a correlation between reduced ECD and hexagonality in eyes with more severe stages of DR; however, no significant alterations were observed in CV and CCT.

Explaining the variations in the literature regarding the impact of T2DM on endothelial parameters is challenging. However, the most plausible explanation is that the reports included patients from different ethnicities, and research has

shown that genetic factors may have a significant influence on the regulation of retinal endothelial function and the development of DR.<sup>36</sup> It is worth noting that all of our patients had some degree of DR, with over 54% experiencing moderate-to-severe DR, which likely contributed to the observed changes in endothelial parameters. This suggestion is supported by many research that T2DM can have several negative effects on endothelial parameters by reducing nitric oxide bioavailability therefore impairing vasodilation,<sup>37</sup> and increasing the production of reactive oxygen species, leading to oxidative stress.<sup>17</sup>

Given the high prevalence of diabetes and DR, our study underlines the need for comprehensive corneal health evaluation in all diabetic patients at any stage of DR to facilitate better surgical outcomes and reduce the likelihood of corneal complications. As a result, preoperative corneal evaluations become essential, particularly in the Libyan population where a considerable number of cataract surgeries are performed annually.

## Conclusion

This study found significant reductions in corneal ECD and hexagonality, as well as increased cell size variability and CCT in individuals with type 2 diabetes. The severity and duration of diabetes, as well as the severity of DR, were found to be correlated with these changes. Therefore, it is crucial for diabetic patients to undergo comprehensive corneal health evaluations to improve surgical outcomes and minimize DM complications in the eye.

## Limitation of Our Study

This study's limitations include a small sample size, potentially limiting the generalizability of findings to a larger population. The exclusion of patients undergoing pan-retinal photocoagulation might have affected the sample size and its representation of DR patients. Being hospital-based, it may not fully reflect the broader population with T2DM. This study's relatively short duration may not capture long-term effects on corneal health. Finally, the lack of ethnic diversity might limit the findings' applicability to diverse populations affected by T2DM.

### Conflict of Interest

None declared.

## References

- Cameron JD. Corneal reaction to injury. In: Krachmer JH, Mannis MJ, Holland EJ, eds. *Cornea*. 2nd ed. Philadelphia, PA: Elsevier Mosby; 2005:115–133
- Bonanno JA. Molecular mechanisms underlying the corneal endothelial pump. *Exp Eye Res* 2012;95(01):2–7
- Polse KA, Brand RJ, Cohen SR, Guillon M. Hypoxic effects on corneal morphology and function. *Invest Ophthalmol Vis Sci* 1990;31(08):1542–1554
- Joyce NC. Proliferative capacity of corneal endothelial cells. *Exp Eye Res* 2012;95(01):16–23
- McCarey BE, Edelhauser HF, Lynn MJ. Review of corneal endothelial specular microscopy for FDA clinical trials of refractive procedures, surgical devices, and new intraocular drugs and solutions. *Cornea* 2008;27(01):1–16
- Hua R, Liu L, Wang X, et al. Comparison of specular microscopy and confocal microscopy for evaluation of corneal endothelial morphology. *Cornea* 2020;39(09):1109–1114
- Zhou W, Li Y, Zhang X, Liang X, Liu Z. Evaluation of corneal endothelial cell density and morphology in cataract patients with type 2 diabetes. *J Diabetes Complications* 2015;29(01):63–68
- Ang ET, Cruzat A, Sabogal-Paz L, et al. Corneal endothelial cell morphology and function in early Fuchs' endothelial corneal dystrophy. *Cornea* 2018;37(10):1316–1321
- Scheler A, Spoerl E, Boehm AG. Effect of age on corneal biomechanics and corneal applanation tonometry. *J Ophthalmol* 2017;2017:7535363
- Gangaraju R, Massoudi D, Azar DT. Alterations in corneal endothelial cell density in patients with diabetes mellitus: a systematic review and meta-analysis. *Cornea* 2016;35(11):1437–1441
- Wolffsohn JS, Hall RC, Dewhurst N, et al. The influence of soft contact lens wear on the corneal endothelium. *Cont Lens Anterior Eye* 2017;40(03):153–163
- American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2014;37(Suppl 1):S81–S90
- International Diabetes Federation. *IDF Diabetes Atlas*. 9th ed. Brussels, Belgium: International Diabetes Federation; 2019
- Matheus AS, Tannus LR, Cobas RA, Palma CC, Negrato CA, Gomes MB. Impact of diabetes on cardiovascular disease: an update. *Int J Hypertens* 2013;2013:653789. Doi: 10.1155/2013/653789. Epub 2013 Mar 4. PMID: 23533715; PMCID: PMC3603160
- Ting DSJ, Cheung GCM, Wong TY. Diabetic retinopathy: global prevalence, major risk factors, screening practices and public health challenges: a review. *Clin Exp Ophthalmol* 2016;44(04):260–277
- Saeedi P, Petersohn I, Salpea P, et al; IDF Diabetes Atlas Committee. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract* 2019;157:107843
- Hassan N. A. A review of the formation and role of advanced glycosylated end products and their receptor in the progression of diabetic complications. *Pure Appl Biol* 2023;12(01):241–251(PAB)
- Elkady B, Elmassy A, Nageeb G. Corneal endothelial cells in diabetes mellitus. *Int J Ophthalmol* 2018;11(02):299–303
- Gavriş M, et al. Central corneal thickness in diabetic patients: a metaanalysis. *J Ophthalmol* 2020;2020:9541252
- Hoang QV, et al. Central corneal thickness in patients with diabetes. *J Diabetes Res* 2017;2017:2935021
- Choo M, Prakash K, Samsudin A, Soong T, Ramli N, Kadir A. Corneal changes in type II diabetes mellitus in Malaysia. *Int J Ophthalmol* 2010;3(03):234–236
- Mencucci R, Favuzza E, Boccalini C, et al. Corneal endothelium evaluation in type II diabetes mellitus. *J Ophthalmol* 2020;2020:1–6
- El-Agamy A, Alsubaie S, Alabduljalil T, et al. Assessment of corneal endothelial morphology in patients with diabetes mellitus: a cross-sectional observational study. *BMC Ophthalmol* 2021;21(01):237
- Pekel G, et al. Corneal biomechanical properties in diabetic retinopathy. *J Ophthalmol* 2018;2018:5795387
- Güler M, Bilal S, Akçay E, Bayraktar S. The effects of diabetic retinopathy severity on corneal parameters in patients with type 2 diabetes mellitus. *Arq Bras Oftalmol* 2021;84(02):143–148
- Elfturi A, Ali M, Elmagrehi E, et al. Prevalence of diabetes mellitus and its associated risk factors in Libya: a nationwide population-based survey. *Prim Care Diabetes* 2020;14(03):259–265
- Jha A, Verma A, Alagorie AR. Association of severity of diabetic retinopathy with corneal endothelial and thickness changes in patients with diabetes mellitus. *Eye (Lond)* 2022;36(06):1202–1208

- 28 Storr-Paulsen A, Singh A, Jeppesen H, Norregaard JC, Thulesen J. Corneal endothelial morphology and central thickness in patients with type II diabetes mellitus. *Acta Ophthalmol* 2014;92(02):158–160
- 29 Leelawongtawun W, Suphachearaphan W, Kampitak K, Leelawongtawun R. A comparative study of corneal endothelial structure between diabetes and non-diabetes. *J Med Assoc Thai* 2015;98(05):484–488
- 30 Islam QU, Mehboob MA, Amin ZA. Comparison of corneal morphological characteristics between diabetic and non diabetic population. *Pak J Med Sci* 2017;33(06):1307–1311
- 31 Taşlı NG, Icel E, Karakurt Y, et al. The findings of corneal specular microscopy in patients with type-2 diabetes mellitus. *BMC Ophthalmol* 2020;20(01):214
- 32 Kim YJ, Kim TG. The effects of type 2 diabetes mellitus on the corneal endothelium and central corneal thickness. *Sci Rep* 2021;11(01):8324
- 33 Altay Y, Dadaci Z, Erdem U. Corneal parameters in diabetes mellitus and their correlation with the level of retinopathy. *Clin Ophthalmol* 2014;8:107–111
- 34 Sudhir RR, Raman R, Sharma T. Changes in the corneal endothelial cell density and morphology in patients with type 2 diabetes mellitus: a population-based study, Sankara Nethralaya Diabetic Retinopathy and Molecular Genetics Study (SN-DREAMS, Report 23). *Cornea* 2012;31(10):1119–1122
- 35 Durukan I. Corneal endothelial changes in type 2 diabetes mellitus relative to diabetic retinopathy. *Clin Exp Optom* 2020;103(04):474–478
- 36 Fickweiler W, Mitzner M, Jacoba CMP, Sun JK. Circulatory Biomarkers and Diabetic Retinopathy in Racial and Ethnic Populations. *Semin Ophthalmol* 2023;38(05):446–456
- 37 Jian Q, Wu Y, Zhang F. Metabolomics in diabetic retinopathy: from potential biomarkers to molecular basis of oxidative stress. *Cells* 2022;11(19):3005