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Original Article

Changes in corneal endothelial cell density and central corneal thickness in patients with type 2 diabetes mellitus

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Abstract

Background and objectives: The corneal endothelium is essential for maintaining corneal transparency and visual function. Chronic hyperglycaemia in type 2 diabetes mellitus (T2DM) can impair endothelial pump activity, resulting in reduced endothelial cell density (ECD) and increased central corneal thickness (CCT). Because endothelial cells do not regenerate, progressive cell loss may lead to irreversible endothelial decompensation. This study evaluates the association of T2DM with ECD and CCT and examines how these parameters relate to diabetes duration, glycaemic control (HbA1c) and diabetic retinopathy (DR).

Materials and methods: This cross-sectional study, conducted at BIRDEM General Hospital, included 86 patients with T2DM and 86 individuals in the non-diabetic group. The T2DM group was subdivided by DR status (no DR, non-proliferative DR and proliferative DR). Following standard ophthalmic examinations, specular microscopy was performed to measure ECD and CCT in the right eye. Data were analyzedusing t-test, ANOVA, correlation analysis and multivariate regression (SPSS version 26).

Results: Individuals with T2DM demonstrated a significant loss of endothelial cells, with mean ECD 275 cells/mm² lower than the non-diabetic group (2585·18 ± 263·12 vs 2860·06 ± 244·45 cells/mm²; p<0·001). CCT did not differ significantly between groups (527·60 ± 32·93 vs 524·37 ± 40·81 µm; p=0·568). In multivariate regression, age contributed to a loss of 21·25 cells/mm² per year (p<0·001), while T2DM independently accounted for an additional loss of 191·12 cells/mm² (p<0·001). Increasing intraocular pressure (IOP) had no significant effect on ECD (loss of 15·17 cells/mm² per mmHg; p=0·277).

Conclusion: T2DM is associated with substantial endothelial cell loss, which is accentuated by longer disease duration, poor glycaemic control and the presence of DR, whereas CCT remains unaffected.

Introduction

Diabetes Mellitus (DM) is a critical global health issue requiring continuous medical supervision and comprehensive risk-reduction strategies beyond glucose control [1]. With the growing prevalence of DM, many organs, including the eyes, are increasingly

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vulnerable to damage. While Diabetic Retinopathy (DR) is the most widely recognized ocular complication, DM also affects the cornea, particularly the corneal endothelium, causing both structural and functional alterations. These changes may include reduced endothelial cell density (ECD), altered cell size and shape andincreased central corneal thickness (CCT), all of which have the potential to impair vision [2]. The cornea, a transparent tissue essential for transmitting light to the retina and forming clear retinal images, consists of five layers, with the endothelium playing a pivotal role in maintaining corneal transparency [3].

Endothelial cells have the highest density at birth but decline naturally with age at approximately 0.6% per year [4], a process compensated by increased cell size (polymegathism) and variation in cell shape (pleomorphism) [5]. DM exacerbates these age-related changes by causing delayed wound healing, reduced corneal sensitivity and endothelial dysfunction [2]. Persistent hyperglycaemia contributes to endothelial abnormalities such as decreased ECD, increased CCT, reduced hexagonality, polymegathism and pleomorphism [6]. Elevated blood glucose induces aldose reductase activity, leading to sorbitol accumulation, deposition of advanced glycation end products (AGEs), endothelial cell loss and impaired corneal transparency [7]. Furthermore, inflammation and oxidative stress associated with DR can disrupt corneal physiology, further altering endothelial cell morphology and function [8].

Pan-retinal photocoagulation (PRP), a standard treatment for proliferative diabetic retinopathy (PDR), may also lead to endothelial cell damage, reflected by reduced ECD and increased CCT [9]. Specular microscopy, an optical technique that records corneal endothelial reflections, consistently demonstrates reduced ECD, decreased cell hexagonality and increased CCT in individuals with DM [10]. Cataract surgery adds further risk to endothelial integrity, particularly in older patients with DM, where the natural decline in ECD is compounded by diabetes-related endothelial vulnerability [11].

Data on diabetes-related corneal endothelial alterations in Bangladesh remain limited despite the growing burden of T2DM. Corneal endothelial cell loss and morphological abnormalities may compromise corneal transparency and increase the risk of adverse outcomes following intraocular surgery. Assessment of ECD, CV, HEX and CCT therefore has important clinical relevance in diabetic populations. This study evaluated corneal endothelial characteristics in patients with T2DM compared with non-diabetic individuals and examined their associations with DM duration, HbA1c, DR and relevant ocular parameters.

Materials and methods

This cross-sectional study was conducted at BIRDEM General Hospital between September 2022 and August 2023 and included 86 adults with T2DM and 86 individuals in the non-diabetic group, recruited through consecutive sampling. Participants were aged 35–60 years and provided written informed consent. Inclusion required confirmed T2DM for the diabetic group and normal fasting glucose and HbA1c values for the non-diabetic group.In contrast, individuals with ocular surface disease, corneal endothelial dystrophy, previous ocular trauma or surgery, elevated intraocular pressure (IOP), contact lens wear, ocular infection, long-term topical medication use, or high myopia (>–6.0 D) were excluded. Ethical approval was obtained from the ethical review committee of BIRDEM General Hospital. All participants underwent comprehensive right-eye evaluations including specular microscopy (NIDEK CEM-30, USA), best-corrected visual acuity testing, intraocular pressure measurement andslit-lamp and fundus examination.Specular microscopy parameters included endothelial cell density, average cell area, coefficient of variation, percentage of hexagonal cells and central corneal thickness. Fasting glucose, 2-hour postprandial glucose and HbA1c levels of the individuals were assessed as well. Diabetic participants were categorized into no diabetic retinopathy (no-DR), non-proliferative DR and proliferative DR groups. Data were analyzed using SPSS version 26 with Student's t test and ANOVA for continuous variables, χ^2 test for categorical variables and multiple regression analyses to assess relationships, with significance defined as $p<0.05$.

Results

The mean age was significantly higher in the type 2 diabetes mellitus (T2DM) group compared with the non-diabetic group (50.88 ± 5.71 vs. 48.35 ± 7.14 years, p = 0.011). Age-group distribution (p = 0.564) and gender (p = 0.360) did not differ significantly between groups. HbA1c (%)—reported as mean ± SD—was markedly higher among individuals with T2DM (9.24 ± 2.14%) compared with non-diabetics (5.91 ± 0.16%, p < 0.001). IOP showed no significant between-group difference (14.07 ± 1.33 vs. 13.70 ± 1.39mmHg, p = 0.075)(Table-1).

Table-1: *Demographic characteristics, HbA1c and IOP of the study population (n=172)*

Variables	T2DM (n=86)	No DM (n=86)	p value
Age			
35-44 years	22(25.6)	22 (25.6)	
45-54 years	31 (36.0)	25 (29.1)	0.564
≥ 55 years	33 (38.4)	39 (45.3)	
Mean ± SD (years)	50.88 ± 5.71	48.35 ± 7.14	0.011
Gender			
Male	41 (47.7)	48 (55.8)	0.360
Female	45 (52.3)	38 (44.2)	
HbA1c(%)	9.24 ± 2.14	5.91 ± 0.16	<0.001
IOP(mmHg)	14.07 ± 1.33	13.70 ± 1.39	0.075

Values are expressed as n (%) for categorical variables and mean ± SD for continuous variables.
Statistical tests used: Chi-square test for categorical variables; Independent samples t-test for continuous variables.
Prediabetics were also included among no DM group.

The ECD was significantly lower in the T2DM group (2585.18 ± 263.12 cells/mm²) compared to the non-diabetic group (2860.06 ± 244.45 cells/mm², p<0.001). The coefficient of variation (CV) was significantly higher in the T2DM group (31.89 ± 4.70%) than in the non-diabetic group (30.19 ± 4.20%, p=0.013). The percentage of hexagonal cells (HEX) was significantly lower in the T2DM group (64.52 ± 6.36%) compared to the non-diabetic group (66.95 ± 5.84%, p=0.010). However, there was no significant difference in CCT between the groups (527.60 ± 32.93 µm vs. 524.37 ± 40.81 µm, p=0.568) (Table-2).

Table-2: *Comparison of endothelial cell characteristics between two groups.*

Parameters	T2DM (n=86)	No DM (n=86)	p-value
ECD (cells/mm^2)	2585.18 ± 263.12	2860.06 ± 244.45	<0.001
CV (%)	31.89 ± 4.70	30.19 ± 4.20	0.013
HEX (%)	64.52 ± 6.36	66.95 ± 5.84	0.010
CCT (µm)	527.60 ± 32.93	524.37 ± 40.81	0.568

Values are expressed as mean ± SD. Independent samples t-test was performed.

ECD was significantly lower in patients with >10 years of T2DM (2486.69 ± 260.93) compared to ≤10 years (2679.20 ± 231.13, p<0.001). Similarly, ECD declined in those with HbA1c >7.5% (2532.28 ± 262.60) versus ≤7.5% (2730.08 ± 207.82, p=0.002). Among DR subgroups, ECD was lowest in PDR cases (2215.27 ± 213.53), followed by NPDR (2589.35 ± 235.67) and no DR (2669.27 ± 213.23, p<0.001). CCT differences were not statistically significant for duration of DM (p=0.299), HbA1c levels (p=0.197), or DR status (p=0.929) (Table-3).

Table-3: *Association of ECD and CCT with the duration of T2DM, HbA1c levels and DR status.*

T2DM (n=86)	ECD (cells/mm^2)	P value	CCT (µm)	P value
Duration of DM				
≤ 10 years (n=44)	2679.20 ± 231.13	<0.001	531.22 ± 34.73	0.299
> 10 years (n=42)	2486.69 ± 260.93		523.80 ± 30.89	
HbA1c				
≤ 7.5 % (n=23)	2730.08 ± 207.82	0.002	535.21 ± 36.06	0.197
> 7.5 % (n=63)	2532.28 ± 262.60		524.82 ± 31.56	
Diabetic Retinopathy status				
No DR (n=47)	2669.27 ± 213.23		527.57 ± 30.46	
NPDR (n=28)	2589.35 ± 235.67	<0.001	526.35 ± 37.35	0.929
PDR (n=11)	2215.27 ± 213.53		530.90 ± 34.16	

Values expressed as mean ± SD. Statistical test: Independent samples t-test and one-way ANOVA.
Cut-offs reflect established clinical thresholds: HbA1c >7.5% for suboptimal control and duration >10 years for long-standing diabetes.

Multivariate regression analysis demonstrated that increasing age was significantly associated with a decrease in ECD (B = -21.247, p<0.001), with each year contributing to a reduction of approximately 21 cells/mm². T2DM was also a significant independent predictor of lower ECD (B = -191.124, p<0.001), indicating a reduction of 191 cells/mm² in diabetic individuals compared to non-diabetic participants. Intraocular pressure (IOP) did not show a statistically significant association with ECD (B = -15.174, p=0.277) (Table-4).

Table-4: *Multivariate regression analysis of factors influencing corneal ECD (n=172)*

Variables	B	SE	β	p-value	95% CI for B
(Constant)	4070.7	200.1		<0.001	3675.6 to 4465.8
Age (year)	-21.247	2.931	-0.463	<0.001	-27.0 to -15.460
T2DM	-191.124	36.593	-0.318	<0.001	-263.4 to -118.9
IOP (mmHg)	-15.174	13.917	-0.069	0.277	-42.6 to 12.3

a. Dependent variable: ECD (cells/mm²)

Discussion

The corneal endothelium plays a central role in maintaining stromal deturgescence and optical clarity and its dysfunction poses a risk for postoperative complications and vision loss. Chronic hyperglycaemia in type 2 diabetes mellitus (T2DM) contributes to oxidative stress, accumulation of advanced glycation endproducts and microvascular compromise, all of which may impair endothelial structure and function [1]. In this study, patients with T2DM demonstrated significantly reduced endothelial cell density (ECD) compared with non-diabetic controls, consistent with previous reports by Kim and Kim [12] and Jha et al. [13]. These findings underscore the susceptibility of endothelial cells to metabolic injury and long-term hyperglycaemic exposure.

Importantly, T2DM was also associated with a higher coefficient of variation (CV) and reduced hexagonality. These parameters are clinically meaningful: increased CV reflects greater variability in cell size (polymegathism), while reduced hexagonality indicates loss of the normal hexagonal architecture (pleomorphism). Both changes signal endothelial stress and reduced physiological reserve, even before substantial ECD loss becomes clinically apparent. Similar alterations have been reported in other diabetic cohorts [12,13], whereas

Kadri et al. found no significant differences [14], suggesting possible heterogeneity related to ethnicity, glycaemic control, imaging technique, or disease duration.

Central corneal thickness (CCT) did not differ significantly between groups, aligning with findings from Çolak et al. [15] and Sudhir et al. [16]. However, some studies, such as Taşlı et al. [17], have reported increased CCT in diabetic individuals, possibly reflecting endothelial pump dysfunction in more advanced disease. The absence of CCT changes in our cohort suggests relatively preserved deturgescence despite measurable morphological endothelial alterations.

Longer diabetes duration (≥10 years) and poorer glycaemic control (HbA1c >7.5%) were associated with significantly lower ECD, consistent with the cumulative impact of chronic hyperglycaemia reported by Storr-Paulsen et al. [18]. However, other studies such as Choo et al. [19] have shown fewerclear associations, highlighting inter-individual variability in metabolic susceptibility. Additionally, ECD was lowest in patients with proliferative diabetic retinopathy (PDR), echoing the findings of Jha et al. [13], although El-Agamy et al. [20] reported no significant association. These discrepancies warrant further investigation into the shared microvascular pathways linking retinopathy severity and endothelial degeneration.

T2DM is associated with significant corneal endothelial alterations, including reduced ECD and increased morphological variability, reflecting diminished endothelial reserve even without increased CCT. These subclinical changes may predispose patients to postoperative corneal oedema and delayed visual recovery, underscoring the value of routine endothelial assessment for surgical planning and risk stratification, particularly in patients with long-standing DM, poor glycaemic control, or DR.

In conclusion, endothelial compromise can occur despite normal CCT and incorporating corneal endothelial evaluation into routine ocular care may optimise perioperative management.

Recommendations

Multicentre prospective studies with long-term follow-up are needed to confirm these findings.

Limitations

This study's cross-sectional, single-centre design and moderate sample size limit causal inference and generalisability and longitudinal changes or postoperative outcomes were not assessed.

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Conflict of interest

The authors declare that they have no financial, personal, or institutional conflicts of interest that could have influenced the preparation or outcomes of this study.

Ethical Approval

Ethical approval was obtained from the Ethical Review Committee of BIRDEM Academy.

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