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Original Research

THE CORRELATION OF HBA1C AND DIABETIC RETINOPATHY WITH CORNEAL ENDOTHELIAL PARAMETER IN PATIENTS WITH TYPE-II DIABETES MELLITUS

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ABSTRACT

IIntroduction: This study investigated the relationship between HbA1c levels and diabetic retinopathy (DR) status with central corneal thickness (CCT), endothelial cell density (ECD), coefficient of variation in cell area (CV), and hexagonality (HEX) in patients with type 2 diabetes mellitus (T2DM).

Methods: This cross-sectional study evaluated 101 eyes of patients with T2DM recruited at Dr. Saiful Anwar General Hospital between July 2023 and February 2024. The study population consisted of 68 eyes with DR and 33 eyes without DR. Corneal endothelial characteristics were assessed using a NIDEK CEM-530 non-contact specular microscope.

Results: Increasing HbA1c levels were correlated with lower ECD (r=-0.340, p<0.001) and lower Hex (r=-0.294, p=0.003), whereas no significant correlations were observed with CCT (r=-0.095, p=0.344) or CV (r=0.007, p=0.948). The presence of DR was correlated with increased CV (r=0.324, p=0.001) and reduced Hex (r=-0.333, p=0.001), while its associations with CCT (r=-0.061, p=0.546) and ECD (r=-0.175, p=0.081) were not statistically significant.

Conclusion: In patients with T2DM, HbA1c levels and DR status were associated with specific measures of corneal endothelial density and morphology. These findings describe differences within a diabetic population.

Keywords: HbA1c, diabetic retinopathy, central corneal thickness, corneal endothelial cell density, type-II diabetes mellitus

Introduction

The World Health Organization (WHO) estimates that the number of individuals with diabetes mellitus (DM) in Indonesia will increase markedly from 8.4 million in 2000 to approximately 21.3 million by 2030. The prevalence of DM among adults aged 18–99 years was estimated at 8.4% in 2017 and is projected to rise to 9.9% by 2045. Likewise, the International Diabetes Federation (IDF) reported that the number of people living with DM in Indonesia is expected to grow from 9.1 million in 2014 to 14.1 million by 2035.[1]

Diabetes mellitus is associated with a broad spectrum of macrovascular and microvascular complications, including diabetic keratopathy, which may impair corneal endothelial function. The corneal endothelium is essential for maintaining corneal deturgescence and optical transparency through its barrier and pump functions.[2] Compared with non-diabetic individuals, patients with diabetes mellitus exhibit significant alterations in corneal endothelial morphology and function. These changes include reduced endothelial cell density, increased central corneal thickness, and greater variability in endothelial cell size. In the presence of endothelial dysfunction, marked corneal thickening, particularly a central corneal thickness exceeding 640 µm, has been associated with an increased risk of postoperative corneal decompensation.[3,4]

However, evidence regarding these associations remains inconsistent. Some studies have reported that central corneal thickness is approximately 6.50 µm greater in individuals with diabetes than in non-diabetic controls, with further increases observed in association with higher serum glucose and HbA1c levels.[5] The mean density of corneal endothelial cells was −175 cells/mm2 less in patients with diabetes. The density of endothelial cells with polymegathism was significantly greater in the eyes of patients with diabetes.

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Corneal endothelial cell polymegathism and pleomorphism appear to be positively associated with type II DM. Cell density was significantly lower in eyes with diabetic retinopathy compared to eyes without diabetic retinopathy.[4] However, evidence regarding these associations remains inconsistent. Some studies have reported that central corneal thickness is approximately 6.50 µm greater in individuals with diabetes than in non-diabetic controls, with further increases observed in association with higher serum glucose and HbA1c levels..[6–9] In contrast, other studies have found no significant association between diabetes mellitus and corneal endothelial parameters, regardless of the presence or absence of diabetic retinopathy. [10–12]

Investigations addressing these relationships in the Indonesian population remain limited. Therefore, the present study was undertaken to characterize the associations between HbA1c levels and diabetic retinopathy status with central corneal thickness (CCT), endothelial cell density (ECD), coefficient of variation (CV), and hexagonality (HEX) in patients with type 2 diabetes mellitus (T2DM). The analysis was specifically focused on interindividual differences within the diabetic population.

Methods

This cross-sectional study included 101 eyes with type 2 diabetes mellitus (T2DM). The study was conducted after ethical approval from the Faculty of Medicine, Universitas Brawijaya (No. 400/062/K.3/102.7/2023). All participants were recruited from the outpatient clinic at Dr. Saiful Anwar General Hospital, Malang, Indonesia, from July 2023 to February 2024 and provided written informed consent before enrollment. Each eye was evaluated separately according to the eligibility criteria. If both eyes met the inclusion and exclusion criteria, both eyes were included; if only one eye was eligible, only that eye was included. A total of 134 patients were screened, of whom 101 eligible eyes were included in the final analysis. T2DM was identified by the Internal Medicine Department. Participants were categorized into those with diabetic retinopathy (n=68) and those without diabetic retinopathy (n=33). Data on diabetes duration and treatment history were also collected.

Exclusion criteria comprised ocular or treatment-related factors that could compromise corneal endothelial health. These included elevated intraocular pressure, defined as an intraocular pressure >21 mmHg, a cup-to-disc ratio >0.6, or an inter-eye cup-to-disc ratio asymmetry ≥0.2; a history of ocular trauma; corneal degeneration, dystrophy, or other corneal abnormalities; previous intraocular surgery, including cataract surgery or trabeculectomy; prior refractive procedures such as LASIK, LASEK, refractive lens exchange (RLE), SMILE, or ReLEx SMILE; previous ocular laser treatment, including panretinal photocoagulation, laser peripheral iridotomy, Nd:YAG laser, grid laser, or argon laser; a history of ocular infection; and contact lens use.

All participants underwent a comprehensive ophthalmic examination comprising visual acuity assessment using a Snellen chart, anterior segment evaluation by slit-lamp biomicroscopy, intraocular pressure measurement by applanation tonometry, and dilated fundus examination using indirect ophthalmoscopy.

Clinical data regarding the duration of diabetes mellitus and glycemic control were also obtained, with HbA1c levels measured at the time of presentation. Corneal endothelial assessment was performed using a non-contact specular microscope (NIDEK CEM-530). The recorded endothelial parameters included central corneal thickness (CCT; µm), endothelial cell density (ECD; cells/mm²), coefficient of variation in cell size (CV; %), and percentage of hexagonal cells (Hex; %), measured using the instrument's automated tracking system.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 25.0. Quantitative variables were summarized as mean ± standard deviation. The distribution of continuous variables was evaluated using the Shapiro–Wilk test, with a p value <0.05 considered indicative of a significant departure from normality. Both central corneal thickness (CCT) and endothelial cell density (ECD) demonstrated normal distributions in the diabetic retinopathy (DR) and non-DR groups (CCT: p=0.068 and p=0.151, respectively; ECD: p=0.361 and p=0.058, respectively). In contrast, the coefficient of variation (CV) was non-normally distributed in both groups (p=0.001 and p=0.046, respectively), whereas hexagonality (Hex) showed a non-normal distribution in the DR group (p<0.001).

Comparisons of CCT and ECD were performed using independent-samples t tests, whereas CV and Hex were analyzed using the Mann–Whitney U test according to diabetic retinopathy status and diabetes duration. Associations between corneal endothelial parameters and either HbA1c levels or diabetic retinopathy status were evaluated using Spearman's rank correlation analysis. Statistical significance was defined as a two-sided p value <0.05.

Result

A total of 101 eyes were included in the study, comprising 68 eyes with diabetic retinopathy (DR) and 33 eyes without DR. The mean participant age was 54.49 ± 7.90 years, and 58 participants (57.4%) were female. The mean duration of diabetes mellitus was 6.91 ± 6.25 years. Baseline demographic and clinical characteristics are summarized in Table 1.

Table 1. Characteristics of the Diabetes Mellitus Group According to Sex, Age, Disease Duration, and Retinopathy Status

Variable	DM group, *N* (%)
Gender	
Male	43 (42.6%)
Female	58 (57.4%)
Age [years]	
26-35	3 (3.0%)
36-45	7 (6.9%)
46-55	49 (48.5%)
56-65	33 (32.7%)
> 65	9 (8.9%)
Duration [years]	
< 10 years	71 (70.3%)
≥ 10 years	30 (29.7%)
Therapy	
Oral Anti Diabetic	72 (71.3%)
Insulin	22 (21.8%)
Combination	7 (6.9%)
DR Status	
No Diabetic Retinopathy	33 (32.7%)
Diabetic Retinopathy	68 (67.3%)

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Corneal endothelial characteristics stratified by diabetes duration are presented in Table 2. No statistically significant differences were observed in CCT, ECD, CV, or Hex between participants with a diabetes duration of <10 years and those with a duration of ≥10 years (all p>0.05).

Table 3 summarizes the corneal endothelial parameters according to diabetic retinopathy status. Eyes with diabetic retinopathy demonstrated a significantly higher CV compared with eyes without diabetic retinopathy (31.94 ± 4.55% vs 29.03 ± 3.14%, p=0.001) and a significantly lower Hex value (65.38 ± 5.84% vs 69.09 ± 4.10%, p=0.001). In contrast, no statistically significant differences were observed between the groups in CCT (p=0.588) or ECD (p=0.111).

Table 2. Comparison of corneal endothelial parameters according to diabetes duration.

	Duration	Mean±SD	*P* Value
CCT [µm]	< 10 years	547.46±27.28	0.123
	≥ 10 years	559.70±38.65	
ECD [cells/mm²]	< 10 years	2712.61±306	0.541
	≥ 10 years	2669.63±354	
CV [%]	< 10 years	31.07±4.43	0.873
	≥ 10 years	30.80±4.21	
Hex [%]	< 10 years	66.61±5.22	0.69
	≥ 10 years	66.57±6.48	

DM diabetes mellitus, CCT central corneal thickness, ECD endothelial cell density, CV coefficient of variation of cell area, Hex Hexagonal, DR diabetic retinopathy

Table 4 presents the relationships between corneal endothelial parameters and either HbA1c levels or diabetic retinopathy status. Higher HbA1c levels were significantly associated with lower ECD (r=-0.340, p<0.001) and reduced Hex (r=-0.294, p=0.003), whereas no significant associations were identified with CCT (r=-0.095, p=0.344) or CV (r=0.007, p=0.948).

Diabetic retinopathy status was significantly associated with increased CV (r=0.324, p=0.001) and decreased Hex (r=-0.333, p=0.001), while its associations with CCT (r=-0.061, p=0.546) and ECD (r=-0.175, p=0.081) were not statistically significant.

Table 3. Correlation of corneal endothelial parameters according to diabetic retinopathy status.

	DR Status	Mean±SD	*P* Value
CCT [µm]	No Diabetic Retinopathy	553.55±33.28	0.588
	Diabetic Retinopathy	549.91±30.62	
ECD [cells/mm²]	No Diabetic Retinopathy	2772.94±239.16	0.111
	Diabetic Retinopathy	2664.37±349.21	
CV [%]	No Diabetic Retinopathy	29.03±3.14	0.001
	Diabetic Retinopathy	31.94±4.55	
Hex [%]	No Diabetic Retinopathy	69.09±4.10	0.001
	Diabetic Retinopathy	65.38±5.84	

DM diabetes mellitus, CCT central corneal thickness, ECD endothelial cell density, CV coefficient of variation of cell area, Hex Hexagonal, DR diabetic retinopathy.

Table 4. Correlation of Corneal Endothelial Parameters with HbA1c Levels and Diabetic Retinopathy Status.

Factor in DM group	CCT [µm]	ECD [cells/mm²]	CV [%]	Hex [%]
HbA1c (%)				
R value	-0.095	-0.34	0.007	-0.294
P value	0.344	<0.001	0.948	0.003
DR status				
R value	-0.061	-0.175	0.324	-0.333
P value	0.546	0.081	0.001	0.001

DM diabetes mellitus, CCT central corneal thickness, ECD endothelial cell density, CV coefficient of variation of cell area, Hex Hexagonal, DR diabetic retinopathy

Discussion

The main findings of this study varied according to the specific corneal endothelial parameter assessed. Among patients with T2DM, the presence of diabetic retinopathy was associated with increased CV and reduced HEX, whereas no significant differences in CCT or ECD were observed according to DR status. Higher HbA1c levels were similarly associated with lower ECD and Hex, but showed no significant relationship with CCT or CV. Furthermore, none of the endothelial parameters differed significantly between groups stratified by diabetes duration. Therefore, numerical differences that did not reach statistical significance should not be interpreted as evidence of a directional effect. As the study did not include a non-diabetic control group, the findings should be regarded as associations observed within the T2DM population rather than as evidence of a direct effect of diabetes on the corneal endothelium.

Hyperglycemia exerts widespread cytotoxic effects and contributes to structural and functional alterations in multiple ocular tissues, particularly the retina and cornea. In diabetic retinopathy, chronic hyperglycemia and oxidative stress may promote leukocyte-mediated endothelial injury and increased vascular permeability, changes that can precede pericyte loss. Subsequent pericyte depletion may contribute to retinal hypoxia, resulting in upregulation of vascular endothelial growth factor (VEGF), further disruption of vascular permeability, increased intercellular adhesion molecule-1 (ICAM-1) expression, and endothelial cellular responses. In the cornea, hyperglycemia may impair endothelial homeostasis through several mechanisms, including disruption of apical intercellular junctions, compromise of the corneal barrier, and alterations in cellular permeability. In addition, increased aldose reductase activity may lead to intracellular sorbitol accumulation, thereby promoting osmotic stress and endothelial cell swelling in diabetic corneas.[10-16]

In the present study, diabetic retinopathy was associated with alterations in corneal endothelial morphology, characterized by a higher coefficient of variation and lower hexagonality, whereas no significant associations were observed with central corneal thickness or endothelial cell density. This pattern has not been uniformly reported in previous studies. Jha et al., for example, found that increasing severity of diabetic retinopathy was associated with significantly lower ECD (p<0.001) and Hex (p=0.001), together with higher CV (p=0.007) and greater CCT (p=0.01).[6]

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Similarly, Geilani et al. reported that increasing severity of diabetic retinopathy was associated with progressive corneal endothelial alterations, including significant reductions in endothelial cell density and hexagonality, accompanied by increases in the coefficient of variation and central corneal thickness.[17] Canan et al. reported that both the duration of diabetes mellitus and the presence of diabetic retinopathy were significantly associated with central corneal thickness.[18] El-Agamy et al. similarly reported no statistically significant relationships between the duration of diabetes mellitus, HbA1c concentration, or the severity of diabetic retinopathy and corneal endothelial morphological parameters, including central corneal thickness, coefficient of variation in cell size, hexagonality, and endothelial cell density.[19]

Endothelial cell density alone may not adequately reflect the functional status or degree of stress of the corneal endothelium, even in eyes with markedly reduced cell counts below 500 cells/mm^2. Morphological indices such as polymegathism and pleomorphism have been proposed as more sensitive indicators of endothelial cellular stress. An increased coefficient of variation in cell size together with a reduced proportion of hexagonal cells reflects greater heterogeneity and disruption of the normal cellular arrangement, which may be associated with impaired endothelial barrier and pump functions. Accordingly, assessment of polymegathism and pleomorphism may provide additional information regarding endothelial compromise that is not fully captured by endothelial cell density alone.[20,21]

HbA1c showed no significant association with CCT or CV, but was significantly and inversely correlated with ECD and Hex. These findings suggest that the relationship between glycemic status and corneal endothelial characteristics in this cohort was parameter-specific rather than reflective of a uniform change across all measured indices. Although this pattern may indicate a potential association between chronic hyperglycemia and endothelial cellular stress, the cross-sectional nature of the study precludes any inference of causality.

HbA1c may therefore provide a systemic indicator associated with specific corneal endothelial characteristics, particularly ECD and Hex, whereas diabetic retinopathy status appears to be more closely related to CV and Hex. Chronic hyperglycemia has been proposed to impair endothelial Na^+/K^+-ATPase activity, a key component of corneal endothelial pump function, thereby contributing to alterations in cellular morphology and permeability. Consequently, evaluation of corneal endothelial parameters may have clinical value in the preoperative assessment of patients undergoing cataract or refractive surgery. In addition, elevated glucose levels may increase aldose reductase activity and intracellular sorbitol accumulation, promoting osmotic cell swelling and potentially increasing the risk of corneal edema, particularly when endothelial cell density is reduced..[4,18,22,23] However, neither HbA1c nor DR status was associated with all endothelial parameters, and DR status was not significantly associated with either ECD or CCT. These clinical variables should therefore not be considered substitutes for specular microscopy when direct assessment of endothelial density and morphology is clinically required, including preoperative evaluation before intraocular surgery.

Patients with T2DM may still warrant careful preoperative endothelial assessment and use of endothelial-protective surgical strategies when clinically indicated. However, this study did not compare diabetic with non-diabetic patients and did not evaluate postoperative outcomes; therefore, it cannot determine whether diabetes itself increases the risk of endothelial decompensation after intraocular surgery.

LIMITATIONS

Several methodological limitations should be acknowledged. First, the cross-sectional design does not permit assessment of temporal relationships or causal associations. Second, because no non-diabetic control group was included, the study was unable to determine the independent effect of diabetes on corneal endothelial parameters; therefore, the findings are limited to variations within the T2DM population according to HbA1c level and diabetic retinopathy status. Third, the single-center outpatient recruitment may have introduced selection bias and may restrict the generalizability of the results to other populations and clinical settings. Fourth, diabetic retinopathy was categorized only according to its presence or absence, without further stratification by disease severity. Future multicenter studies should incorporate non-diabetic comparison groups, classify diabetic retinopathy according to severity, and employ multivariable analytical approaches to account for potential confounding factors.

Conclusion

In patients with T2DM, increasing HbA1c levels were significantly associated with reduced endothelial cell density and hexagonality, while no significant relationships were observed with CCT or CV. Diabetic retinopathy status was associated with higher CV and lower Hex, but not significantly with CCT or ECD. These findings identify parameter-specific associations within a diabetic population and should not be interpreted as evidence of the effect of diabetes itself. HbA1c and diabetic retinopathy status may provide useful complementary clinical information when assessing corneal endothelial health, but they should not replace direct corneal endothelial assessment by specular microscopy when such evaluation is clinically indicated.

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