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ORIGINAL ARTICLE

Corneal endothelial pathology and thickening in early diabetes mellitus

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Abstract

Background: The corneal endothelium is crucial for maintaining corneal integrity. Diabetic patients often exhibit corneal endothelial alterations, but the onset and nature of these changes, particularly in early-stage disease with good glycemic control, remain unclear.

Methods: This retrospective case–control study involved 312 eyes from 180 patients (118 diabetic and 194 non-diabetic). Modern specular microscopy was employed to assess corneal endothelial properties, including endothelial cell density (ECD), central corneal thickness (CCT), and glycemic control indices. Statistical analyses, including Pearson's correlation and multiple regressions, were conducted to explore associations and differences between the groups.

Results: Diabetic subjects demonstrated significantly lower ECD (2467.8 ± 334.5 vs. 2553.5 ± 289.2, $P = 0.028$) and higher CCT compared to non-diabetics. Notably, a borderline association was found between diabetes duration and CCT. While significant correlations were observed among specular microscopy findings, diabetes duration, and glycemic indices, no notable associations were found with HbA1C or fasting glucose levels. Adjustment for confounders revealed consistent differences in corneal parameters between diabetic and non-diabetic groups.

Conclusions: This retrospective study unveils distinct corneal endothelial alterations in diabetic patients, even in early stages with good glycemic control. Lower ECD and increased CCT in diabetic subjects highlight potential vulnerabilities in corneal health. These findings emphasize the importance of vigilant monitoring and tailored interventions, especially during cataract surgery, to safeguard the corneal endothelium and optimize outcomes in diabetic populations.

Introduction

The corneal endothelium is crucial for maintaining corneal thickness, hydration, and transparency. Comprising hexagonal cells without *in vivo* mitotic capability,[1] its cell counts can decrease due to several factors, such as normal aging and cataract surgery. Compensatory mechanisms involve the expansion and migration of remaining endothelial cells, resulting in irregular shapes. When cell counts drop critically low, bullous keratopathy may develop, leading to severe vision loss.[2]

Diabetes mellitus has been linked to endothelial cell loss and irregularities in shape, such as elevated polymegathism and pleomorphism.[3-5] Additionally, diabetic patients have been observed to exhibit elevated central corneal thickness (CCT) compared to non-diabetics.[4,6] Effective glycemic control in diabetic patients could be pivotal in surgical risk management. Hyperglycemia alone can induce endothelial changes significant enough to elevate a routine surgery into a high-risk case.[7]

A question arises regarding whether corneal endothelial pathology and increased CCT manifest in the early stages of well-controlled diabetes or if they characterize late or poorly managed stages of the disease. To our knowledge, no studies employing modern specular microscopy have addressed this issue. Consequently, we conducted an assessment to compare endothelial properties and CCT between non-diabetic patients

and those recently diagnosed with type 2 diabetes, exhibiting good glycemic control.

Methods

This study conformed to the tenets of the Declaration of Helsinki and was approved by the institutional review board.

Study design

This is a retrospective case–control study, conducted at the Ophthalmology Department at the Soroka University Medical Center; Beer Sheva, Israel.

Patients

The key inclusion criteria encompassed adult patients aged 50–90 years diagnosed with type-2 diabetes mellitus according to the WHO criteria,[8] within the preceding 10 years.

The control group comprised non-diabetic patients matched for age and gender distribution. Exclusion criteria encompassed patients with a history of previous intraocular or ocular surface surgery, contact lens wear, trauma, intraocular inflammation, corneal infections, or diagnosed corneal pathology (excluding dry eye). Additionally, patients were excluded if their diabetes status was not documented in the records. All subjects underwent a comprehensive ocular examination, which included a review of medical history, slit-lamp examination of the anterior segment, fundus examination, and specular microscopy. Diabetic retinopathy classification followed the Early Treatment Diabetic Retinopathy Study standardization protocols.

Assessment

Specular microscopy was conducted using the SP-02 specular non-contact microscope (C.S.O., Scandicci; Firenze, Italy), a device commonly employed in both clinical practice and research.[9] High-quality images of the corneal endothelium's center were captured, followed by the software's automatic marking of contiguous endothelial cells and subsequent specular analysis. The image analysis utilized the corner method. To mitigate sampling error, patients with fewer than 125 cells/frame captured by the specular microscope were excluded.[10]

We calculated endothelial cell density (ECD), CCT, and coefficient of variation (CV). Additionally, pleomorphism, which reflects the variation in cell shape, was calculated as the fraction of hexagonal cells.

Statistical analysis

We conducted statistical analyses using the Statistical Package for the Social Sciences (SPSS) software (version 17.0, SPSS, Inc., Chicago, IL). Pearson's correlation was utilized for parametric data, while Spearman's correlation was applied for non-parametric data. To compare means, we employed the t-test and one-way ANOVA test. To account for potential confounders such as age, gender, and intrapersonal data variation, a multiple regression analysis was conducted using the non-standardized B coefficient.[11] A $P \leq 0.05$ was considered statistically significant.

Results

The study encompassed a total of 312 eyes from 180 patients: 118 eyes in the diabetic group and 194 eyes in the control group (non-diabetic patients).

The overall mean age observed was 70.9 ± 7.8 years. Both groups exhibited similar age and sex distributions, with no statistically significant differences found (P = 0.49; P = 0.08, respectively). Details regarding the demographic characteristics of the study population are summarized in Table 1.

The study group exhibited a mean diabetes duration of 7.8 years and an HBA1C level of 7.2%. Additionally, most patients in the study group did not have diabetic retinopathy. In the control group, the mean fasting glucose level was 89.7 ± 12.45 mg/dL. Details regarding diabetes duration, glycemic control indices, and retinopathy data are summarized in Table 2.

Pearson correlation analysis revealed a significant correlation among specular microscopy findings, diabetes duration, and levels of fasting glucose and hemoglobin A1C. Additionally, statistically significant differences were observed between the study groups. Raw data underwent adjustment for various factors including age, gender, eye laterality (right vs. left), IOP, retinopathy, and whether one or both eyes were evaluated. A summary of the multiple linear regression analysis is presented in Table 3.

The adjusted mean ECD was significantly lower in the diabetic group compared to the control (2467.8 ± 334.5 and 2553.5 ± 289.2, respectively; P = 0.028). Additionally, adjusted CCT and cell area were significantly greater in the diabetic group. A borderline association was observed between adjusted CCT and diabetes duration. However, no statistically significant differences were found in the CV or the percentage of hexagonal cells. HbA1C and fasting glucose levels did not exhibit associations with any of the assessed parameters. Details of corneal and endothelial indices are provided in Table 4.

Discussion

Corneal endothelial cells in diabetic patients demonstrate both quantitative and qualitative anomalies. Previous studies have consistently indicated reduced cell density in diabetic individuals.[5,12] Additionally, diabetic patients exhibit distinct

Table 1: Baseline and demographic data

Parameter	Diabetic	Non-diabetic	*P*-value
Gender			
Male	37	31	0.49
Female	55	57	
Age	71.9±7.7	70.3±7.9	0.08

Chi-square test and Unpaired t test were performed to detect statistically significant differences between groups in gender and age, respectively

Table 2: Diabetes characteristics and retinopathy data

Parameter	Diabetic	Non-diabetic	*P*-value
Diabetes Duration (Mean±SD)	7.8±6.2 years	-	
HbA1C % (Mean±SD)	7.2%±1.2%	-	
Fasting Glucose (Mean±SD)	135±47.5 mg/dL	89.7±12.45 mg/dL	<0.0001
Diabetic retinopathy	None 88%	-	
	Non-proliferative 9%		
	Proliferative 3%		

Paired *t* test was performed to detect statistically significant differences between groups in fasting glucose. SD standard deviation. Bold for *P*-value <0.05.

Table 3: Summary of multiple linear regression analysis

Parameter	Diabetes diagnosis		Diabetes duration	
	B regression value	*P*-value	B regression value	*P*-value
ECD	−79.1	0.03	4.9	0.39
CCT (μm)	11.34	0.03	1.51	0.05
Cell Area (μm^2)	15.1	0.021	1.27	0.29
CoV (%)	1.1	0.2	0.14	0.9
Hexa (%)	−0.34	0.68	−0.59	0.612

ECD: Endothelial cell density (mean±standard deviation), CCT: Central corneal thickness, CoV: Coefficient of variation and *Hexa* percentage of hexagonal cells.

Table 4: Adjusted corneal and endothelial characteristics

Parameter	Diabetic	Non-diabetic	*P*-value*
ECD	2467.8±334.5	2553.5±289.2	0.028
CCT (μm)	558.8±48.8	547.1±44.6	0.034
Cell Area (μm^2)	412.9±68	396.7±46.6	0.021
CoV (%)	42.9±7.3	41.8±7.3	0.198
Hexa (%)	49.3±7.0	49.6±7.0	0.678

ECD: Endothelial cell density (mean±standard deviation), CCT: Central corneal thickness, CoV: Coefficient of variation and *Hexa* percentage of hexagonal cells. *Paired *t* test was performed to detect statistically significant differences between groups

morphological alterations compared to non-diabetics, including increased CCT,[4,7,12] elevated CV,[4] and a lower percentage of hexagonal cells.[1]

Several biochemical and histologic mechanisms may underlie these findings. Biochemically, at least four processes occur in diabetic conditions: Increased polyol pathway flux, activation of protein kinase C, elevated hexosamine pathway flux, and the formation of advanced glycation end-products (AGEs).[13] Among these, AGEs are relatively well understood. Prolonged hyperglycemia triggers a series of non-enzymatic reactions between glucose and proteins, leading to the production of AGEs.[14] These compounds detrimentally affect the corneal endothelium through dual mechanisms: Intracellular or extracellular accumulation[15] and activation of cell membrane receptors, resulting in the production of harmful cytokines.[16] AGEs have been associated with endothelial dysfunctions in diabetes, including conditions like Fuchs' dystrophy.[17,18] Furthermore, they have been identified in Descemet's membrane, potentially contributing to abnormal endothelial adhesion and subsequent anomalies in endothelial shape and function.[19]

Histologically, corneal deposits within Descemet's membrane and thickening of Descemet's membrane have been reported.[20]

While most studies indicate that poorly controlled diabetic patients exhibit qualitative and quantitative alterations in the corneal endothelium,[21] there is an ongoing debate regarding whether these changes manifest in early stages or in well-controlled diabetes.

In our study, we observed significant differences in mean ECD values and CCT between diabetic patients and non-diabetics. Additionally, we identified a statistically borderline association between diabetes duration and CCT.

It is important to note several limitations in this study. One of the primary weaknesses is its retrospective case–control design rather than a prospective longitudinal study. Additionally, the studied population was clinic based rather than population based.

Nevertheless, we anticipate that due to the large sample size and meticulous adjustment for multiple potential confounders, our study will provide a comprehensive portrayal of corneal changes within the diabetic population.

Conclusion

In conclusion, diabetic subjects exhibit lower ECD and higher CCT, even in early stages with good glycemic control. Therefore, during cataract surgery in diabetic patients, safeguarding the corneal endothelium by minimizing phaco time and utilizing dispersive viscoelastic substances could prove beneficial.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. The first draft of the manuscript was written by Konstantin Gushansky, and all authors provided comments on previous versions of the manuscript. Finally, all authors read and approved the final manuscript.

Ethics Approval

Approval was obtained from the ethics committee of Ben-Gurion University. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

References

1. Tang Y, Chen X, Zhang X, Tang Q, Liu S, Yao K. Clinical evaluation of corneal changes after phacoemulsification in diabetic and non-diabetic cataract patients, a systematic review and meta-analysis. Sci Rep 2017;7:14128.
2. Tuft SJ, Coster DJ. The corneal endothelium. Eye (Lond) 1990;4:389-424.
3. Schultz RO, Matsuda M, Yee RW, Edelhauser HF, Schultz KJ. Corneal endothelial changes in type I and type II diabetes mellitus. Am J Ophthalmol 1984;98:401-10.
4. Lee JS, Oum BS, Choi HY, Lee JE, Cho BM. Differences in corneal thickness and corneal endothelium related to duration in diabetes. Eye (Lond) 2006;20:315-8.
5. Shenoy R, Khandekar R, Bialasiewicz A, Al Muniri A. Corneal endothelium in patients with diabetes mellitus: A historical cohort study. Eur J Ophthalmol 2009;19:369-75.
6. Lesiewska-Junk H, Kałuzny J, Malukiewicz-Wiśniewska G. Long-term evaluation of endothelial cell loss after phacoemulsification. Eur J Ophthalmol 2002;12:30-3.
7. Su DH, Wong TY, Wong WL, Saw SM, Tan DT, Shen SY, *et al.* Diabetes, hyperglycemia, and central corneal thickness: The Singapore Malay Eye Study. Ophthalmology 2008;115:964-8.e1.
8. American Association of Diabetes. Standards of medical care in diabetes. Diabetes Care 2010;33:S11-61.
9. González-Méijome JM, Jorge J, Queirós A, Peixoto-de-Matos SC, Parafita MA. Two single descriptors of endothelial polymegethism and pleomorphism. Graefes Arch Clin Exp Ophthalmol 2010;248:1159-66.
10. Abib FC, Holzchuh R, Schaefer A, Schaefer T, Godois R. The endothelial sample size analysis in corneal specular microscopy clinical examinations. Cornea 2012;31:546-50.
11. Daniel WW. Biostatistics: A Foundation for Analysis in the Health Sciences. 9th ed. New York: John Wiley & Sons; 2009.
12. Mathew PT, David S, Thomas N. Endothelial cell loss and central corneal thickness in patients with and without diabetes after manual small incision cataract surgery. Cornea 2011;30:424-8.
13. Hammes HP. Pathophysiological mechanisms of diabetic angiopathy. J Diabetes Complications 2003;17:16-9.
14. Kalousová M, Zima T, Tesar V, Stípek S, Sulková S. Advanced glycation end products in clinical nephrology. Kidney Blood Press Res 2004;27:18-28.
15. Bos DC, de Ranitz-Greven WL, de Valk HW. Advanced glycation end products, measured as skin autofluorescence and diabetes complications: A systematic review. Diabetes Technol Ther 2011;13:773-9.
16. Thornalley PJ. Cell activation by glycated proteins. AGE receptors, receptor recognition factors and functional classification of AGEs. Cell Mol Biol (Noisy-le-grand) 1998;44:1013-23.
17. Amano S, Kaji Y, Mimura T. Biology of corneal endothelial cells *in vivo* and *in vitro*. Jpn J Ophthalmol 2010;54:211-4.
18. Wang Z, Handa JT, Green WR, Stark WJ, Weinberg RS, Jun AS. Advanced glycation end products and receptors in Fuchs' dystrophy corneas undergoing Descemet's stripping with endothelial keratoplasty. Ophthalmology 2007;114:1453-60.
19. Kaji Y, Amano S, Usui T, Suzuki K, Tanaka S, Oshika T, *et al.* Advanced glycation end products in Descemet's membrane and their effect on corneal endothelial cell. Curr Eye Res 2001;23:469-77.
20. Rehany U, Ishii Y, Lahav M, Rumelt S. Ultrastructural changes in corneas of diabetic patients: An electron-microscopy study. Cornea 2000;19:534-8.
21. Calvo-Maroto AM, Cerviño A, Perez-Cambrodí RJ, García-Lázaro S, Sanchis-Gimeno JA. Quantitative corneal anatomy: Evaluation of the effect of diabetes duration on the endothelial cell density and corneal thickness. Ophthalmic Physiol Opt 2015;35:293-8.

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