· Original article ·

Changes of corneal endothelial cells and nuclear density in cataract patients with type 2 diabetes

Liu Yueqi, Liu Gaoqin*, Chen Zhigang, Han Xue, Lu Peirong*

引用:刘乐麒,刘高勤,陈志刚,等.2 型糖尿病白内障患者角膜内皮细胞及核密度变化.国际眼科杂志, 2025, 25(9): 1392-1398.

Foundation item: National Natural Science Foundation of China (No.82271113)

Department of Ophthalmology, the First Affiliated Hospital of Soochow University, Suzhou 215006, Jiangsu Province, China

* Co-first authors: Liu Yueqi and Liu Gaoqin

Correspondence to: Lu Peirong. Department of Ophthalmology, the First Affiliated Hospital of Soochow University, Suzhou 215006, Jiangsu Province, China. lupeirong@suda.edu.cn

Received: 2024-11-22 Accepted: 2025-06-13

2 型糖尿病白内障患者角膜内皮细胞及核密度变化

刘乐麒*,刘高勤*,陈志刚,韩 雪,陆培荣

基金项目:国家自然科学基金(No.82271113)

作者单位:(215006)中国江苏省苏州市,苏州大学附属第一医院眼科

*:刘乐麒和刘高勤对本文贡献一致。

作者简介:刘乐麒,毕业于苏州大学,硕士,研究方向:眼科学;刘高勤,毕业于苏州大学,医学博士,副研究员,研究方向:新生血管性眼病。

通讯作者:陆培荣,毕业于日本金泽大学,医学博士,主任医师,教授,研究方向:新生血管性眼病. lupeirong@suda.edu.cn

摘要

目的:探讨 2 型糖尿病白内障患者角膜内皮细胞(CEC)及核密度(ND)的特征,并评估血糖相关指标的影响。

方法:纳入 2023 年 7 月至 2024 年 7 月在我院行白内障手术的患者 187 例 187 眼,采用非接触式镜面显微镜测量 CEC,通过 IOLMaster 700 测量 ND。根据糖化血红蛋白(HbA1c)和空腹血糖(FBG)水平对 187 名参与者进行分层。采用相关性分析和多元线性回归分析阐明糖尿病状态与眼部参数之间的关联。测量 52 名参与者房水中抗坏血酸(AA)的浓度。

结果:与对照组相比,糖尿病组最大内皮细胞大小增大、内皮细胞密度(ECD)减小、六边形细胞比例降低、ND 增大以及角膜顶点等效球面度数(Scv)降低($P<0.05$)。相关性分析结果显示,CEC 和 ND 的变化与空腹血糖(FBG)、糖化血红蛋白(HbA1c)水平及糖尿病病程显著相关($P<0.05$)。在 52 名参与者中,糖尿病患者房水中的 AA 水平较低,表明抗氧化能力减弱。

结论:糖尿病状态可显著影响白内障患者的角膜最大细胞大小、六边形细胞比例及 ND,这可能与房水中总抗氧化能力下降有关。

关键词:角膜内皮细胞;六边形细胞比例;核密度;抗坏血酸;血糖

Abstract

• AIM: To investigate the characteristics of corneal endothelial cells (CEC) and nuclear density (ND) in cataract patients with type 2 diabetes and to assess the impact of blood glucose related indicators.

• METHODS: A total of 187 cases (187 eyes) that underwent cataract surgery at our hospital from July 2023 to July 2024 were enrolled. CEC were measured using a non-contact specular microscope. ND was measured through IOLMaster 700. A total of 187 participants were further stratified based on glycosylated hemoglobin (HbA1c) and fasting blood glucose (FBG) levels. Correlation analyses and multiple linear regression analyses were used to elucidate the association between diabetic status and ocular parameters. We measured the concentrations of ascorbic acid (AA) in the aqueous humor of 52 participants.

• RESULTS: Compared to the control group, the diabetic group exhibited larger maximum endothelial cell size, lower endothelial cell density (ECD), a reduced proportion of hexagonal cells, higher ND, and lower corneal vertex equivalent spherical power (Scv; $P<0.05$). Correlation analysis revealed those changes of CEC and ND were significantly associated with the level of FBG, HbA1c, and the duration of diabetes ($P<0.05$). Among 52 participants, diabetic patients had lower levels of AA in their aqueous humor, indicating a diminished antioxidant ability.

• CONCLUSION: Diabetic state can significantly influence corneal maximum cell size, hexagonal cell ratio and ND in cataract patients, potentially linked to a decrease in total antioxidant capacity of the aqueous humor.

• KEYWORDS: corneal endothelium cell; hexagonal cell ratio; nuclear density; ascorbic acid; blood glucose

DOI:10.3980/j.issn.1672-5123.2025.9.02

Citation: Liu YQ, Liu GQ, Chen ZG, et al. Changes of corneal endothelial cells and nuclear density in cataract patients with type 2 diabetes. Guoji Yanke Zazhi (Int Eye Sci), 2025, 25(9): 1392-1398.

INTRODUCTION

Owing to global demographic shifts towards an older population cohort worldwide, there has a steady increase in the prevalence of diabetes—a multifaceted metabolic disorder characterized by persistent hyperglycemia-rendering it one among the foremost critical public health concerns world globally. It is estimated that by 2040, the worldwide diabetic population will reach 615 million individuals[1]. Diabetes has been associated with detrimental impacts on multiple organ systems including ocular complications such as cataracts due to chronic hyperglycemia-induced formation of advanced glycation end products, heightened oxidative stress, and enhanced activation within the polyol pathway[2]. Given that cataracts are prone to early onset, higher frequency occurrence, and predominantly affect those within their working years, cataract surgery holds particular significance for diabetic patients[3].

Diabetic patients face an elevated risk of corneal epithelial fragility, defects, abnormal wound healing, and heightened susceptibility to infectious corneal ulcers[4-5]. The direct physical impact of hyperglycemia on corneal hydration can alter the morphology of corneal layers, including refractive index, thickness, and topography, thereby compromising corneal transparency[6]. *In vitro* studies have demonstrated that hyperglycemia may result in loss and dysfunction of corneal endothelial cells (CEC) through sustained activation of endoplasmic reticulum stress[7]. Therefore, a thorough preoperative assessment is essential for accurately planning and performing surgery in cataract patients with diabetes.

The corneal endothelium is directly exposed to the aqueous humor, a transparent and viscous fluid that fills the anterior chamber of the eye. This fluid not only supplies nutrients but also removes metabolic waste from the avascular tissues of the eye. Typically, aqueous humor contains ascorbic acid (AA), which functions as a UV filter, a direct free radical scavenger of free radicals, and an antioxidant regulator[8]. Additionally, AA inhibits induced apoptosis and lipid peroxidation[9]. A prior study identified AA as the primary contributor to the total antioxidant capacity (TAC) of aqueous humor, playing a crucial role in maintaining adequate corneal endothelial cell density (ECD)[10].

In addition, prior research findings indicate that individuals afflicted with type 1 diabetes exhibit increased thickness in their lenses and along with reduced refractive indices when compared to control cohorts[11-12], whereas elderly Chinese patients suffering from type 2 diabetes demonstrate augmented lens thickness coupled with elevated magnification levels[13]. The influence exerted by type 2 diabetes on ocular biometry remains contentious[14], and investigations into alterations pertaining nuclear density (ND) remain unexplored.

Therefore, the present study aimed to systematically evaluate the impact of oxidative stress on the number and structure of CEC, ND of the lens, and the concentration of antioxidant factors in the aqueous humor, with an emphasis on elucidating the potential interrelationships among these parameters.

PARTICIPANTS AND METHODS

Ethical Approval The study protocol was approval by the Ethics Committee of the First Affiliated Hospital of Soochow University (No.2024434) and adhered to principles outlined in the Declaration of Helsinki.

Patients The cohort comprised 187 participants (187 eyes) with nuclear cataracts who underwent cataract surgery at the First Affiliated Hospital of Soochow University between July 2023 and July 2024. Among them, 86 patients with type 2 diabetes and cataracts were assigned to the diabetic group, while the control group consisted of 101 patients with cataracts but without diabetes. The subsequent part of the study involved the collection of aqueous humor samples from 52 participants (52 eyes) who underwent surgery at the same hospital from April 2024 to July 2024. AA concentrations in these samples were quantified.

Participants were considered eligible for inclusion in the study if they met the following criteria: nuclear cataracts classified as stage III to IV according to the Lens Opacities Classification System III, an axial length (AL) ranging from 22 to 25 mm, and corneal astigmatism not exceeding 1.0 diopter. Only individuals with sufficient pupillary dilation to permit a thorough ophthalmic examination and testing were included. Additionally, participants in the diabetes group were required to have a confirmed diagnosis of type 2 diabetes mellitus based on the ICD-10 criteria.

Exclusion criteria included the presence of corneal abnormalities, such as leukoplakia, keratoconus, or pterygium; any history of uveitis, glaucoma, high myopia, retinal disease, ocular trauma, or other significant ocular conditions. Individuals were also excluded if they experienced severe intraoperative complications, including posterior capsular rupture or failure to implant an intraocular lens in the capsular bag. Additionally, patients with a history of tobacco use, alcohol abuse, obesity, or long-term medication use were excluded, as were those with cortical or posterior subcapsular cataracts or incomplete clinical data.

Data Collection and Ocular Examinations All participants underwent a comprehensive, standardized examination conducted by an experienced physician, who sequentially examined and documented the condition of the conjunctiva, lens, iris, anterior chamber, cornea, eyelids, and vitreous for any abnormalities. Following adequate pupillary dilation achieved with compound tropicamide eye drops, the fundus was examined using an indirect ophthalmoscope. The ocular examinations included uncorrected visual acuity, best-corrected visual acuity, intraocular pressure, non-contact specular microscope, the IOLMaster 700, and the anterior segment analysis system. A comprehensive medical history was obtained, including data on participants' diabetes status, disease duration, and current treatment regimen. The same examiner evaluated subjects based on the established inclusion and exclusion criteria, recording and documenting the baseline characteristics of eligible participants.

Non-contact specular microscopy (Topcon SP-3000P,

Japan) with an automatic focus model was employed to select the central corneal area, and the built-in software was utilized for analysis during the examination. Biometric parameters including AL and anterior chamber depth (ACD), were measured using the IOLMaster 700 (Carl Zeiss Meditec AG, Germany), and the corneal vertex equivalent spherical power (Scv) was subsequently calculated. The IOLMaster 700 employs Swept-Source Optical Coherence Tomography technology to conduct continuous B-scan imaging of the examined eye. A 180-degree grayscale image of the lens was selected and imported into the open-source software Image J (National Institutes of Health, USA) for detailed grayscale analysis[15]. The measurement procedure was repeated three times, and the mean value was calculated to determine the ND. The surgeon selected the intraocular lens power based on their own surgical preferences.

Aqueous Humor Collection and TAC Assessment Subsequent to the administration of surface anesthesia during the course of cataract surgery, a 1-mL syringe was employed to procure 50 μL of aqueous humor from the lateral incision, with meticulous attention paid to ensure that no contact was made with the iris, lens, or corneal endothelium. The aqueous humor samples were promptly transferred into pre-labeled sterile 1.5-mL microcentrifuge tubes and stored at -80 ℃ until analysis.

Prior to testing, the assay kit was allowed to reach room temperature, which took approximately 30 min. The thawed aqueous humor samples were subjected to centrifugation at 10 000 rpm for 10 min at 4 ℃. The resulting supernatant was then transferred to a new centrifuge tube and maintained on ice until analysis. The concentration of AA in the aqueous humor was determined using the Ascorbic Acid Microplate Assay Kit (abs580047-96T, Absin, Shanghai, China), following the manufacturer's instructions. The decision to assess TAC in aqueous humor was informed by a review of the literature and previous studies[10].

Statistical Analysis All personal identifiable information obtained during this study remained strictly confidential and was not shared with any external parties. Data measurements underwent exportation utilizing proprietary software embedded within each respective device. Statistical analyses exclusively utilized SPSS software (version 27.0, IBM, USA). The Benjamini-Hochberg method was used to adjust P-values for multiple comparisons to control the false discovery rate. The Kolmogorov-Smirnov test was used to assess the normality of the data distribution. The t-tests were used to compare ocular parameters between groups. ANOVA was used for further subgroup analysis based on fasting blood glucose (FBG) and glycosylated hemoglobin (HbA1c) levels, with variance homogeneity assessed using Bartlett's test. Correlation analyses were performed to investigate the relationships between FBG, HbA1c, diabetes duration and ocular parameters. Pearson correlation coefficients were used for variables that were normally distributed and linearly related; otherwise, Spearman rank correlation coefficients were applied. Multiple linear regression analyses were conducted to explore the predictive value of diabetes-related indicators on outcome variables.

RESULTS

In general, there was an almost equal distribution of female and male participants, with comparable age profiles across both genders ($P>0.05$). Statistically significant variations were found between participant groups regarding FBG and HbA1c levels ($P<0.001$). On average, individuals within the study had been living with diabetes for approximately seven-and-a-half years.

Table 1 provides a summary of ocular biometric findings for the diabetic and control groups. While CEC count long with, minimum, mean and total size showed no notable discrepancies between these two sets ($P>0.05$). However, significant differences were observed in corneal maximum endothelial cell size ($P=0.006$), ECD ($P=0.026$), and hexagonal cell ratio ($P=0.012$).The mean ND in the diabetic group was higher than that in the control group ($P=0.004$). The mean Scv was 113.04 in the diabetic group, compared to 117.38 in the control group, with the difference being statistically significant ($P=0.018$).

We further stratified 187 participants into four groups based on HbA1c level. Participants with HbA1c levels above 7% were classified as having poor glycemic control, and when compared to the control group, they exhibited larger maximum endothelial cells and higher ND. Similarly, all participants were grouped based on their FBG levels. Among those with FBG levels above 7 mmol/L, there was a statistically decrease in hexagonal cell ratio, an increase ND, and decreases in Scv.

Considering the findings from subgroup analyses indicating a potential impact of diabetic state on corneal and lens characteristics, we conducted an in-depth investigation into the association between those ocular parameters and diabetes-related factors, including FBG, HbA1c, and duration of diabetes. Maximum endothelial cell size, hexagonal cell ratio, ND, and Scv were observed to have significant statistical correlations with diabetes-related factors (see Table 2 for correlation coefficients and significance). Among them, ND was moderately correlated with FBG levels ($r=0.314$, $P<0.001$), HbA1c ($r=0.259$, $P<0.001$), and duration of diabetes ($r=0.401$, $P<0.001$).

To evaluate how diabetes duration, FBG, and HbA1c affect ocular parameters, a stepwise multiple linear regression analysis was performed (Table 3). The results revealed that duration of diabetes exerted a substantial influence on corneal maximum endothelial cell size ($r^2=0.027$, $P=0.011$), hexagonal cell ratio ($r^2=0.087$, $P=0.010$) and ND ($r^2=0.158$, $P<0.001$). When all other factors are held constant, corneal maximum endothelial cell size is expected to change by 3.529 μm^2 for every extra year of diabetes. Additionally, the relationship between FBG levels and Scv ($r^2=0.051$, $P=0.017$) was statistically significant. Changes in CEC morphology are more likely to be impacted by long-term hyperglycemia, but changes in corneal refractive function are more likely to be impacted by short-term blood glucose fluctuations.

To investigate potential mechanisms, we measured the concentrations of AA in the aqueous humor of 52 participants to evaluate variations in TAC. As illustrated in Figure 1, there was a statistically significant difference in FBG levels ($P<0.001$). The average AA concentration in the aqueous humor was 0.45±0.15 mmol/L in the diabetic group, as opposed to 0.54±0.14 mmol/L in the control group. A statistically significant difference was observed between these two groups ($P=0.023$).

Table 1 Comparison of ocular data between diabetic group and healthy control $\bar{x}\pm s$

Parameters	Diabetic group ($n=86$)	Healthy control ($n=101$)	P value	P adjusted
Corneal endothelial cell count (cells/mm^2)	100.64±15.31	103.11±17.49	0.310	0.413
Minimum cell size (μm^2)	133.17±49.15	126.96±53.16	0.410	0.447
Maximum cell size (μm^2)	1024.97±228.37	897.10±208.78	<0.001[c]	0.006[b]
Mean cell size (μm^2)	412.69±57.53	395.16±57.73	0.040[a]	0.068
Total cell size (μm^2)	40704.60±4370.99	40144.60±4145.67	0.370	0.444
Endothelial cell density (cells/mm^2)	2451.83±320.01	2573.18±336.88	0.013[a]	0.026[a]
Hexagonal cell ratio (%)	49.00±8.24	53.33±9.82	0.001[b]	0.012[a]
Nuclear density	83.69±13.09	73.29±13.78	<0.001[c]	0.004[b]
Scv	113.04±9.26	117.38±11.91	0.006[b]	0.018[a]

P values were adjusted using the Benjamini-Hochberg FDR correction. Scv: Corneal vertex equivalent spherical power; [a]$P<0.05$; [b]$P<0.01$; [c]$P<0.001$.

Table 2 Analysis of correlation between ocular data, fasting blood glucose, hemoglobin A1c and diabetes duration

Parameters	Fasting blood glucose		Hemoglobin A1c		Diabetes duration	
	r	P	r	P	r	P
Corneal endothelial cell count(cells/mm^2)	−0.035	0.636	0.006	0.934	−0.053	0.474
Minimum cell size (μm^2)	0.008	0.914	0.021	0.772	0.057	0.439
Maximum cell size (μm^2)	0.171	0.019[a]	0.150	0.041[a]	0.287	<0.001[c]
Mean cell size (μm^2)	0.112	0.129	0.083	0.259	0.110	0.133
Total cell size (μm^2)	0.088	0.231	0.043	0.555	0.038	0.604
Endothelial cell density (cells/mm^2)	−0.112	0.127	−0.089	0.224	−0.116	0.115
Hexagonal cell ratio (%)	−0.210	0.004[b]	−0.184	0.012[a]	−0.294	<0.001[c]
Nuclear density	0.314	<0.001[c]	0.259	<0.001[c]	0.401	<0.001[c]
Scv	−0.197	0.007[b]	−0.133	0.070	−0.159	0.030[a]

Scv: Corneal vertex equivalent spherical power; [a]$P<0.05$; [b]$P<0.01$; [c]$P<0.001$.

Table 3 Multivariable analysis for parameters associated with ocular data

Parameters	Ocular data	Beta	SE	t	P	R^2	F	D-W
Diabetes duration	Maximum cell size (μm^2)	3.529	3.652	0.966	0.011[a]	0.027	1.697	1.730
Diabetes duration	Hexagonal cell ratio (%)	−0.004	0.001	−2.607	0.010[a]	0.087	5.841	2.090
Diabetes duration	Nuclear density	0.697	0.216	3.225	<0.001[c]	0.158	11.438	2.179
Fasting blood glucose	Scv	−2.097	0.871	−2.408	0.017[a]	0.051	3.284	1.837

Scv: Corneal vertex equivalent spherical power; SE: Standard deviation; D-W: Durbin-Watson test; [a]$P<0.05$; [c]$P<0.001$.

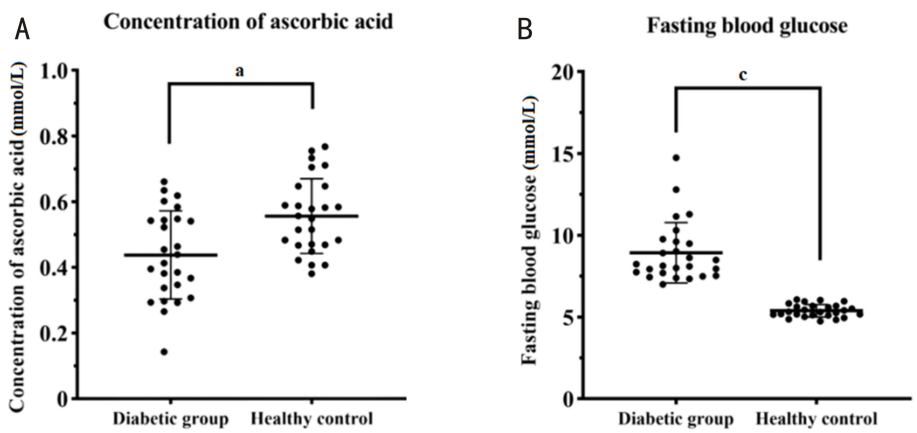

Figure 1 Low concentrations of ascorbic acid are found in the aqueous humor of diabetic patients. A: A Statistical chart comparing ascorbic acid concentrations in the diabetes and healthy control groups; B: A statistical chart comparing fast blood glucose concentrations between diabetes and healthy control groups. [a]$P<0.05$; [c]$P<0.001$.

DISCUSSION

Patients with diabetes mellitus are prone to a variety of ocular complications, including diabetic retinopathy, cataracts, and neovascular glaucoma. Diabetic individuals frequently encounter complications associated with the ocular surface; however, anterior segment complications have not received sufficient attention[16]. Chronic hyperglycemia in diabetes can result in progressive damage to endothelial and epithelial cells, thereby increasing the risk of developing ocular surface diseases such as corneal erosion, persistent epithelial defects, and corneal endothelial decompensation[17].

It is well established that cataracts progress more rapidly in patients with diabetes mellitus. Both cataract surgery and diabetes can exert microscopic effects on the cornea. Extensive research has evaluated the impact of cataract surgery on corneal characteristics in both diabetic and non-diabetic patients[18-20]. These studies indicate that, compared to non-diabetic patients, those with diabetes are more likely to experience significant changes in CEC morphology and corneal thickness. Additionally, foveal thickness tends to increase following cataract phacoemulsification and intraocular lens implantation[19,21]. Misra *et al*[22] found no significant difference in basal epithelial cell density before and after cataract phacoemulsification in both diabetic and non-diabetic patients. One potential explanation for this finding could be variations in the severity and duration of diabetes, as well as differences in image analysis methods. However, diabetic patients with lower initial subbasal nerve density may be more susceptible to diabetic keratopathy. Kang *et al*[23] compared changes in CEC between diabetic and non-diabetic patients following femtosecond laser-assisted cataract surgery. They found no significant difference in CEC changes. At 3 mo post-surgery, no significant difference was observed in the proportion of ECD and hexagonal cells between the two groups. Femtosecond laser-assisted cataract surgery appears to cause less damage to the corneal endothelium in diabetic patients due to its use of lower phacoemulsification energy. However, these studies have several limitations. For instance, there was no analysis of average FBG and HbA1c levels. Additionally, blood glucose control during the perioperative period was not assessed. Further studies are needed to determine whether perioperative blood glucose variability and the course of diabetes influence changes in corneal structures in diabetic patients.

In a study conducted by Yilmaz *et al*[24], corneal density measurements were compared between patients with type 1 diabetes and a control group. The findings revealed that corneal density was significantly higher within the 0-2 mm range across all corneal layers in the diabetic group. Additionally, the corneal volume was found to be significantly increased in the type 1 diabetes group, with a higher average lens density; however, the difference was not statistically significant. Özyol and Özyol[25] reported a positive correlation between the duration of diabetes and total anterior corneal density. Similarly, our study revealed that cataract patients with type 2 diabetes exhibited larger corneal maximum endothelial cell size, lower ECD, and lower hexagonal cell ratio. These alterations were more pronounced in participants with sustained hyperglycemia, as evidenced by larger corneal maximum endothelial cell size in cases with higher HbA1c levels ($7.0\% \leqslant \text{HbA1c} < 8.6\%$). The results of the multivariate analysis indicated that diabetes duration was the most significant factor influencing the corneal maximum endothelial cell size and hexagonal cell ratio.

Prior research has demonstrated elevated lens density among individuals with type 1 diabetes[24], while elderly Chinese individuals with type 2 diabetes exhibited increased lens thickness and magnification[13]. Nevertheless, the influence of blood glucose levels on ND remains inadequately investigated. The subsequent multivariate regression analysis demonstrated that a one-unit increase in diabetes duration was associated with a 0.697-pixel change in ND. A substantial body of research has investigated the association between diabetes and refractive errors, with alterations in myopia and hyperopia documented in diabetic patients[26-27]. In the present study, significant differences were observed in Scv between the two groups. It is noteworthy that the Benjamini-Hochberg method was employed to adjust *P*-values, thereby enhancing the rigor and reliability of the resulting statistical results.

Blood glucose fluctuations, characterized by oscillations between hyperglycemia and hypoglycemia, are considered a key factor in the pathogenesis of diabetic complications. Studies have shown that greater blood glucose variability is strongly associated with heightened oxidative stress, activation of inflammatory responses, and exacerbation of apoptosis[28-29]. Additionally, the eyes of diabetic patients experience a range of metabolic alterations as a result of prolonged hyperglycemia. Elevated aldose reductase activity in diabetic patients leads to the accumulation of polyols, which function as osmotic agents and induce endothelial cell swelling[21]. Dysfunction of the Na+/K+ATPase pump is a key mechanism responsible for the structural and functional changes observed in the corneas of diabetic patients[30]. Furthermore, chronic hyperglycemia promotes an increase in ocular inflammatory mediators, including tumor necrosis factor and interleukin-1, which can disrupt normal corneal structure and potentially lead to cell apoptosis and matrix degradation[31]. Therefore, monitoring the blood glucose fluctuations of cataract patients with type 2 diabetes could help identify the optimal timing for cataract surgery.

Various clinical factors, such as age, ethnicity, body weight, medication use, tobacco consumption, and alcohol abuse, can significantly influence corneal characteristics, particularly the properties of CEC[32-35]. A retrospective cross-sectional study of Han Chinese individuals[36] revealed a strong association between thin corneas (central corneal thickness <500 μm) and decreased ECD, with shorter AL also linked to lower ECD. Furthermore, all findings encompassed ACD as it is closely tied to AL [37-38]. Prior correlation studies have demonstrated a notable positive correlation between AL and

corneal radius, which is postulated to result in corneal flattening and diminished corneal power[39]. In this study, we focused on a cohort of Han Chinese participants with similar age groups, excluding individuals with obesity, tobacco use, alcohol abuse, or long-term medication histories. Furthermore, we found no statistically significant differences in AL, ACD, or central corneal thickness between the diabetic and control groups (all $P>0.05$), minimizing the influence of confounding factors and allowing us to concentrate on the impact of diabetes-related factors.

In a study analyzing 164 human aqueous humor samples[10], significant differences in TAC and AA levels were found between groups with insufficient ECD (ECD < 2100 cells/mm^2) and control groups. TAC and AA are regarded as independent protective factors for endothelial cells. Although the precise mechanism underlying this protective effect remains unclear, previous studies have indicated a potential collaboration between AA and antioxidant proteins, which may contribute to the establishment of a distinctive antioxidant defense system in the aqueous humor[29,40]. In the present study, it was observed that the concentration of AA in the aqueous humor of the diabetic group was significantly lower than that of the control group. This may explain the significant differences in corneal ECD and hexagonal cell ratio observed between the two groups. To the best of our knowledge, this is the inaugural clinical study to document a decrease in AA concentration in aqueous humor in cataract patients with type 2 diabetes.

Our findings offer a novel perspective on ocular alterations among individuals with type 2 diabetes, a topic that has been scarcely explored previously. Nevertheless, there are certain limitations within this study. First, because the primary aim was to observe changes in ND, the inclusion criteria were limited to patients with nuclear cataracts graded III-IV according to the Lens Opacities Classification System III, excluding those with posterior subcapsular cataracts commonly associated with diabetes. Second, the measurement of AA levels in the aqueous humor was conducted on a single occasion, which precludes the ability to discern fluctuations in AA concentrations or progressive alterations in ECD. Furthermore, the study diagnosed type 2 diabetes according to ICD-10 criteria but did not quantify insulin resistance, which limits the comprehensiveness of the research in this regard. To corroborate these findings, further large-scale clinical trials are required.

In conclusion, the findings of our study indicate that FBG, HbA1c, and diabetes duration exert a significant influence on CEC of cataract patients. Lower AA concentrations may be associated with hyperglycemia. This new insight highlights the significance of TAC in the aqueous humor. Patients with poor glycemic control demonstrate deterioration in CEC morphology and acceleration in cataract progression. This results in an elevated risk of surgical complications and postoperative corneal endothelial decompensation. It is therefore recommended that preoperative assessment and stringent glycemic control be employed for cataract patients with type 2 diabetes in order to achieve optimal outcomes.

Conflicts of Interests: Liu YQ, None; Liu GQ, None; Chen ZG, None; Han X, None; Lu PR, None.

Authors' contributions: Liu YQ and Lu PR designed the study; Liu YQ conducted the data analysis and drafted the manuscript; Liu GQ conducted testing on aqueous humor; Chen ZG and Han X searched the literature; Lu PR and Liu GQ polished the article. All authors contributed to the article and approved the submitted version.

REFERENCES

[1] Sacks DB, Arnold M, Bakris GL, et al. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Diabetes Care, 2023,46(10):e151-e199.

[2] Franke S, Dawczynski J, Strobel J, et al. Increased levels of advanced glycation end products in human cataractous lenses. J Cataract Refract Surg, 2003,29(5):998-1004.

[3] Caspersen CJ, Thomas GD, Boseman LA, et al. Aging, diabetes, and the public health system in the United States. Am J Public Health, 2012,102(8):1482-1497.

[4] Gao Y, Zhang Y, Ru YS, *et al*. Ocular surface changes in type II diabetic patients with proliferative diabetic retinopathy. Int J Ophthalmol, 2015,8(2):358-364.

[5] Bikbova G, Oshitari T, Tawada A, et al. Corneal changes in diabetes mellitus. Curr Diabetes Rev, 2012,8(4):294-302.

[6] McNamara NA, Brand RJ, Polse KA,et al. Corneal function during normal and high serum glucose levels in diabetes. Invest Ophthalmol Vis Sci, 1998,39(1):3-17.

[7] Chen C, Zhang B, Xue JF, et al. Pathogenic role of endoplasmic reticulum stress in diabetic corneal endothelial dysfunction. Invest Ophthalmol Vis Sci, 2022,63(3):4.

[8] Ringvold A. The significance of ascorbate in the aqueous humour protection against UV-A and UV-B. Exp Eye Res, 1996,62(3):261-264.

[9] Koliakos GG, Konstas AGP, Schlötzer-Schrehardt U, et al. Ascorbic acid concentration is reduced in the aqueous humor of patients with exfoliation syndrome. Am J Ophthalmol, 2002,134(6):879-883.

[10] Tsao YT, Wu WC, Chen KJ,et al. Analysis of aqueous humor total antioxidant capacity and its correlation with corneal endothelial health. Bioeng Transl Med, 2020,6(2):e10199.

[11] Wiemer NGM, Dubbelman M, Kostense PJ, et al. The influence of diabetes mellitus type 1 and 2 on the thickness, shape, and equivalent refractive index of the human crystalline lens. Ophthalmology, 2008,115(10):1679-1686.

[12] Wiemer NGM, Dubbelman M, Hermans EA, et al. Changes in the internal structure of the human crystalline lens with diabetes mellitus type 1 and type 2. Ophthalmology, 2008,115(11):2017-2023.

[13] Ye LY, He JN, Zhang XJ, et al. The associations of lens power with age, axial length and type 2 diabetes mellitus in Chinese adults aged 50 and above. Eye Vis (Lond), 2020,7(1):57.

[14] Vijayakumar V, Mavathur R, Sharma MNK. Ethnic disparity and increased prevalence of type 2 diabetes among south asians: aetiology and future implications for diabetes prevention and management. Curr Diabetes Rev, 2018,14(6):518-522.

[15] Wang LJ, Li C, Li JQ, et al. Association of lens density quantified by IOLMaster 700 with lenticular myopia in nuclear cataract. Graefe's Arch Clin Exp Ophthalmol, 2022,260(5):1565-1572.

[16] Han SB, Yang HK, Hyon JY. Influence of diabetes mellitus on anterior segment of the eye. Clin Interv Aging, 2018,14:53-63.

[17] Zhu LK, Titone R, Robertson DM. The impact of hyperglycemia on the corneal epithelium: Molecular mechanisms and insight. Ocul Surf, 2019,17(4):644-654.
[18] Tang YZ, Chen XY, Zhang XB, et al. 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.
[19] 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(4):424-428.
[20] Ciorba AL, Roiu G, Abdelhamid AM, et al. Evaluation of the corneal endothelium following cataract surgery in diabetic and non-diabetic patients. Diagnostics, 2023,13(6):1115.
[21] Chen Z, Song FQ, Sun LY, *et al*. Corneal integrity and thickness of central fovea after phacoemulsification surgery in diabetic and nondiabetic cataract patients. Arch Med Sci, 2018,14(4):818-825.
[22] Misra SL, Goh YW, Patel DV, et al. Corneal microstructural changes in nerve fiber, endothelial and epithelial density after cataract surgery in patients with diabetes mellitus. Cornea, 2015, 34(2): 177-181.
[23] Kang KH, Song MY, Kim KY, et al. Corneal endothelial cell changes after femtosecond laser-assisted cataract surgery in diabetic and nondiabetic patients. Eye Contact Lens, 2021,47(12):664-669.
[24] Yilmaz YC, Hayat SC, Ipek SC. Analysis of corneal and lens densitometry changes in patients with type 1 diabetes mellitus. Am J Ophthalmol, 2023,254:23-30.
[25] Özyol P, Özyol E. Assessment of corneal backward light scattering in diabetic patients. Eye Contact Lens, 2018,44(1):S92-S96.
[26] Handa S, Chia A, Htoon HM, et al. Myopia in young patients with type 1 diabetes mellitus. Smedj, 2015,56(8):450-454.
[27] Song E, Qian D-J, Wang S, et al. Refractive error in Chinese with type 2 diabetes and its association with glycaemic control. Clin Exp Optom, 2018,101(2):213-219.
[28] Hirsch IB. Glycemic variability and diabetes complications: does it matter of course it does!. Diabetes Care, 2015,38(8):1610-1614.
[29] Babizhayev MA, Strokov IA, Nosikov VV, et al. The role of oxidative stress in diabetic neuropathy: generation of free radical species in the glycation reaction and gene polymorphisms encoding antioxidant enzymes to genetic susceptibility to diabetic neuropathy in population of type I diabetic patients. Cell Biochem Biophys,2015,71(3):1425-1443.
[30] Gupta S, Gambhir JK, Kalra OP, et al. Association of biomarkers of inflammation and oxidative stress with the risk of chronic kidney disease in Type 2 diabetes mellitus in North Indian population. J Diabetes Complicat, 2013,27(6):548-552.
[31] Eghrari AO, Riazuddin SA, Gottsch JD. Overview of the cornea: structure, function, and development. Prog Mol Biol Transl Sci 2015, 134:7-23.
[32] Zwingelberg SB, Lautwein B, Baar T, et al. The influence of obesity, diabetes mellitus and smoking on fuchs endothelial corneal dystrophy (FECD). Sci Rep, 2024,14:11596.
[33] Karmakar R, Nooshabadi S, Lohmeier J, et al. Alcohol abuse is associated with alterations in corneal endothelial cell morphology. Cornea, 2023,42(4):444-448.
[34] Courson JA, Rumbaut RE, Burns AR. Impact of obesity and age on mouse corneal innervation at the epithelial-stromal interface. Invest Ophthalmol Vis Sci, 2024,65(5):11.
[35] Han S, Mueller C, Wuebbolt C, et al. Selective effects of estradiol on human corneal endothelial cells. Sci Rep, 2023,13:15279.
[36] Miao AO, Lin PM, Qian DJ, et al. Association between endothelial cell density and corneal thickness in medium, short, and long eyes of Han Chinese cataract patients. Am J Ophthalmol, 2024, 262: 10-18.
[37] Yin G, Wang YX, Zheng ZY, et al. Ocular axial length and its associations in Chinese: the Beijing eye study. PLoS One, 2012,7(8): e43172.
[38] Wei L, He WW, Meng JQ, et al. Evaluation of the white-to-white distance in 39, 986 Chinese cataractous eyes. Invest Ophthalmol Vis Sci, 2021,62(1):7.
[39] Cui Y, Meng QL, Guo HK, et al. Biometry and corneal astigmatism in cataract surgery candidates from Southern China. J Cataract Refract Surg, 2014,40(10):1661-1669.
[40] Markoulli M, Flanagan J, Tummanapalli SS, et al. The impact of diabetes on corneal nerve morphology and ocular surface integrity. Ocul Surf, 2018,16(1):45-57.