

## Comparison of Corneal Endothelial Cell Morphology, Intraocular Pressure and Anterior Chamber Parameters in Type 2 Diabetes Mellitus and Healthy Eyes

Özgür Balta<sup>1</sup> and Hande Hüsniye Telek<sup>2\*</sup>

<sup>1</sup>Nafiz Korez Sincan State Hospital, Department of Ophthalmology, Ankara, Turkey

<sup>2</sup>Beytepe Murat Erdi Eker State Hospital, Department of Ophthalmology, Ankara, Turkey

\*Corresponding Author: Hande Hüsniye Telek, Beytepe Murat Erdi Eker State Hospital, Department of Ophthalmology, Ankara, Turkey.

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### Abstract

**Background and Aim:** To evaluate the effects of type II Diabetes Mellitus (DM) on intraocular pressure (IOP), central corneal thickness (CCT), axial length (AL), endothelial cell morphology and anterior chamber parameters.

**Materials and Methods:** In this cross-sectional study, 180 patients with type 2 DM (study group) and 91 healthy subjects (control group) were enrolled. All participants underwent a comprehensive ophthalmic examination, including medical history review, refraction status, best-corrected visual acuity (BCVA), AL, anterior and fundus segment examinations. The anterior chamber angle (ACA), anterior chamber depth (ACD), anterior chamber volume (ACV), CCT, corneal volume (CV) and power of anterior and posterior corneal surface (front Km and back Km) readings were measured by obtained using rotating Scheimpflug camera. Corneal endothelial cell morphology (Endothelial cell density (CD), variation in size of endothelial cells (ECV) and the percentage of hexagonal cells) were analysed using a noncontact specular microscope.

**Results:** There were no significant difference in ACA, ACD, ACV, CV, front Km, AL, CCT ECV, and hexagonality between diabetics and control group ( $p > 0,05$ ). The mean IOP was  $12.0 \pm 2.1$  mmHg in the control group and  $17.0 \pm 2.3$ ,  $17,3 \pm 2.2$  and  $17.1 \pm 2.3$  in the diabetics with the duration of the disease between 1 - 4 years (Group I), 5-9 years (Group II) and over 10 years (Group III), respectively ( $p < 0,001$ ). There were no significant differences among diabetic groups ( $p > 0.05$ ). The mean corneal back Km was higher in diabetics with a disease duration of over 10 years than group 1, group 2 and control group ( $p = 0,026$ ,  $p = 0,005$  and  $p = 0,009$ , respectively). Type II DM groups (group I,II,III) did not differ from the control subjects with regard to the CV of cell size and hexagonality; however, observed a significant decrease in CD [2840 versus 2619 (group I), 2584 (group II), 2532 (group III),  $p = 0,0001$ ] and also found no differences among diabetic groups.

**Conclusion:** This study indicates that DM affects CD, IOP and corneal back Km when compared to healthy subjects.

**Keywords:** Anterior Chamber Parameters; Corneal Endothelial Cell Morphology; Central Corneal Thickness; Diabetes Mellitus; Intraocular Pressure

## **Introduction**

Diabetes mellitus (DM) is a common health problem in the world. The prevalence of Type II diabetes is increasing significantly in all societies, developing, developed and underdeveloped. By the year 2035, it is estimated about 592 million people are estimated to be suffering from diabetes mellitus worldwide while in 2013 there were 382 million people with diabetes mellitus [1]. Type II DM is a systemic disease characterized with the hyperglycemia and affect the eyes in many different ways. There are many ocular complications of diabetes such as diabetic retinopathy, diabetic papillopathy, glaucoma, diabetic keratopathy and cataract progression [2]. Also, dry eye symptoms like to burning or foreign body sensation can cause of the deterioration in quality of life in diabetic patients [2-5]. Diabetes patients have a higher risk of endothelial dysfunction, epithelium healing problems and permanent stromal edema after intraocular surgical procedures and argon laser iridotomy [6-7]. The functional and structural changes consisting of eye in diabetes which is the disease of our century should be known.

DM causes physiological and pathological changes in almost all organ systems due to hyperglycemia effects. One of the most crucial organ systems in which these changes are involved is the eyes. Furthermore, the most common cause of potential blindness in industrialized nations is diabetic retinopathy [8,9]. Moreover, Cohen, *et al.* reported that even patients with impaired fasting glucose (IFG) have higher IOP levels than healthy subjects. Elevated intraocular pressure (IOP) is a risk factor for primary open angle glaucoma which is a leading cause of irreversible blindness [10]. In addition, glycosylation of corneal fibers due to hyperglycemia in patients with DM, results collagen crosslinking and reduces the risk of KCN. In contrast to this general belief, Kosker, *et al.* found a positive association between type 2 DM and the presence and severity of keratoconus [11]. By the increasing popularity of refractive surgery procedures in last 2 decades, pre-operative screening to diagnose subclinical keratoconus and avoid corneal ectasia became more important. Therefore anterior chamber parameters should be analysed carefully in diabetic patients with regard to KCN.

Corneal endothelium is a fundamental factor in maintaining the optical transparency of the cornea. Corneal endothelium structural and functional integrity effects of genetic, race, age, trauma, intraocular surgery and infection [12,13]. Corneal morphologic and functional changes in the diabetic cornea due to the decrease in Na-K ATP ase activity [14].

Pentacam rotating Scheimflug camera is used to examine anterior segment parameters. It could be used to evaluate central corneal thickness (CCT), mean corneal power (Km), corneal curvature (K1,K2), corneal volume (CV), anterior chamber angle (ACA), anterior chamber volume (ACV), and anterior chamber depth (ACD) [15]. Owing to the fact that some anterior segment parameters can provide estimable information for diagnosis and follow-up of keratoconus (KCN), the analysis refractive disorders, accurate calculation of intraocular lens power, and the risk evaluation of glaucoma, these parameters is very important in an ophthalmologic exam [16-19].

In this study, our main goal is to corneal endothelial cell morphology, evaluate anterior segment parameters, CCT, IOP and axial length (AL) in type II diabetic and non-diabetic patients and to relate potential differences to the glycaemic status and duration of diabetes.

## **Materials and Methods**

One hundred and eighty patients with type 2 diabetes mellitus and 91 age- and sex-matched healthy controls were included in the study. Diabetic patients were classified into three groups according to the duration of diabetes: group I (n = 61) with diabetes duration between 1 - 4 years, group II (n = 60) with diabetes duration between 5 - 9 years and group 3 (n = 59) with diabetes duration over 10 years. Diabetic patients are also categorized into two groups according to glycosylated haemoglobin A1c (HbA1c) levels (under or over 7.0%).

This study was approved by the institutional review board of the hospital, and it was in accordance with the principles of the Declaration of Helsinki. All patients gave informed consent before the study. The diagnosis of type II diabetes mellitus was based on criteria of the World Health Organisation (WHO). A definitive clinical and laboratory diagnosis was made based on patient files. All demographic data, records of systemic disease (hypertension, obesity, hypothyroidism, hyperthyroidism, systemic lupus erythematosus, rheumatoid arthritis, scleroderma, liver and kidney diseases), medical history review (oral contraceptives, hormone replacement therapies, antihistamines, anticholinergics, antidepressants), ophthalmological examination results, duration of diabetes, and HbA1c levels were recorded.

Exclusion criteria included BCVA worse than 20/20, spherical  $> \pm 1$  dioptri or cylindrical  $> \pm 1$  dioptri refractive errors, corneal opacities, cataract, pseudoexfoliation syndrome, diabetic retinopathy, history of uveitis, glaucoma, IOL  $> 21$  mmHg, ocular trauma, previous intraocular surgery, presence of systemic diseases such as renal or hepatic dysfunction, obesity, and rheumatological diseases.

All of the patients underwent a comprehensive ophthalmic examination. Refractive defects were measured using an automated refractometer. The best corrected visual acuity was identified for each eye using a Snellen chart. The anterior segment was evaluated through biomicroscopic examination. IOP was measured by Goldmann applanation tonometer and indirect ophthalmoscopy examination was conducted with non-contact fundus lens (SuperField; Volk Optical, Inc., Mentor, OH, USA) after having achieved mydriasis.

Central endothelial cell density (cells/mm<sup>2</sup>) (CD), variation in size of endothelial cells (CV) and the percentage of hexagonal cells were analysed using a noncontact specular microscope (NONCON ROBO Pacy model SP-9000, Konan Medical, Nishinomiya, Japan).

Axial length (AL) was measured using a 10-MHz A/B mode ultrasonography device (Quantel Compact Touch, Quantel Medical, USA) by a single operator with an applanation technique that measured AL from the corneal vertex to the vitreoretinal interface. A minimum of 10 AL recordings were made for each eye and the mean calculated.

The ACA, ACD, ACV, CCT, CV, and Km readings were measured by obtained using rotating Scheimpflug camera (Pentacam version 1.11, Oculus, Wetzlar, Germany). Pentacam system uses rotating Scheimpflug imaging for noncontact and three-dimensional anterior segment assessment. In this study, three-dimensional anterior chamber analysis were used. The head and neck of the patients were placed in the appropriate position. They wanted to open two eyes from the sick and look at the blue target to be measured. Each patient underwent three measurements, the best image was evaluated. Measurements in all patients were conducted with undilated pupils in darkness to standardize all measurements for each patient and a 5 - 10 minutes interval on the same day by a single operator. Because it is known that CCT has been shown to increase overnight and return to baseline within 3 hours of waking, all measurements were done at the same time of the day between 11:00 am and 2:00 pm, at least 3 hours after awakening. Also, only the right eye of each patient was analysed.

### **Statistical analysis**

All statistical tests were performed using SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Normality for continued variables in a group was determined by the Shapiro-Wilk test. Normally distributed measurements were used with the one-way ANOVA and Bonferroni correction were done when  $P < 0.05$  was obtained. Abnormally distributed variables were compared using Kruskal-Wallis test. In case of significant differences, pairwise comparisons were performed using with the Mann-Whitney U test and Bonferroni correction. A probability value of less than 0.05 was considered statistically significant.

### **Results**

Table 1 shows the demographic profile of diabetic patients and controls. There were no difference in both groups in mean age (49.27 vs. 49.85 years;  $P = 0.41$ ) and gender ( $p = 0.70$ ).

	Control	Cases	P- value
	(N = 91)	(N = 180)	
Age	49.27 ± 4.80 (40-60)	49.85 ± 7.14 (40-60)	0.41
(Min-Max)			
Gender (F/M)	50/41	99/81	0.70
HBA1c	None	9,73 ± 3,41	
(Min-Max)		(6-17)	
Diabetes duration	None	6,20 ± 4,20	
(Min-Max)		(2-20)	
Refraction			
Spherical value	-0,2 ± 0,27 (+0,50/-0,75)	-0,2 ± 0,14 (+0,50/-0,75)	<b>0,93</b>
Cylindrical value	-0,1 ± 0,18 (+0,25/-0,25)	-0,1 ± 0,17 (+0,25/-0,25)	<b>0,98</b>
Comorbidity	None	None	

Table 1: Demographic data of cases and controls mean ± SD.

According to duration in diabetes, table 2 compares the anterior segment parameters (CCT, CV, ACA, ACD, ACV, front Km, and back Km), corneal endothelial cell morphology (CD, CV, and hexagonality), IOP and AL measurements in control and diabetic groups. No differences were observed among groups with regard to the mean CCT, CV, ACA, ACD, ACV, AL, front Km, CV, and hexagonality ( $p > 0.05$ ), whereas there was a statistically significant difference in the mean CD, back Km, and IOP values between control and diabetic groups ( $p < 0.05$ ). The mean corneal back Km was higher in group III than in others (6.44 vs 6.25,  $P = 0.009$ ; 6.44 vs 6.28,  $p = 0.026$  and 6.44 vs 6.22,  $p = 0.005$ ); however, there were no differences between groups in other comparison ( $p > 0.05$ ). The mean IOP was higher in all diabetic groups than control group (12.07 vs 17.06, 17.34, 17.18 mm Hg;  $p < 0.05$ ), but there were no differences among diabetic groups ( $p > 0.05$ ). The mean endothelial cell density was lower in control group than diabetic groups (2840.74 vs 2619.60, 2584.40, 2532.79 cell/mm<sup>2</sup>;  $p < 0.05$ ), but there were no differences among diabetic groups ( $p > 0.05$ ).

	Control	Group I	Group II	Group III	P- Value
		(1-4 years)	(5-9 years)	(>10 years)	
Duration of diabetes <sup>a</sup> (years)	-	2.3 ± 1.2	6.4 ± 1.25	13.93 ± 3.53	0.0001 <sup>c</sup>
IOP <sup>b</sup> (mmhg)	12.07 ± 2.18	17.06 ± 2.32	17.34 ± 2.23	17.18 ± 2.33	0.0001 <sup>c</sup>
AL <sup>b</sup> (mm)	22.79 ± 1.61	22.81 ± 1.69	22.75 ± 2.02	22.80 ± 1.81	0.96
CCT <sup>b</sup>	524.1 ± 38.5	532.6 ± 39.3	524.5 ± 29.0	537.2 ± 29.3	0.3
CV <sup>b</sup>	58.75 ± 5.03	58.12 ± 4.17	57.14 ± 4.28	60.11 ± 4.19	0.055
ACAb	34.7 ± 5.1	32.8 ± 7.4	34.4 ± 5.6	33.1 ± 6.3	0.39
ACDb	2.7 ± 0.2	2.6 ± 0.3	2.7 ± 0.3	2.7 ± 0.3	0.26
ACVa	145.80 ± 23.62	142.34 ± 34.93	148.0 ± 31.61	147.27 ± 36.74	0.64
Front Kma	43.18 ± 1.58	43.50 ± 1.31	43.13 ± 1.68	44.01 ± 1.71	0.12

<b>BackKma</b>	6.25 ± 0.28	6.28 ± 0.25	6.22 ± 0.30	6.44 ± 0.32	0.02c
<b><sup>a</sup>CD</b>	2840.74 ± 127.	2619.60 ± 204.	2584.40 ± 151.	2532.79 ± 182.	0.0001 <sup>c</sup>
	2	0	2	3	
<b>(cells/mm2)</b>					
<b><sup>a</sup> CV</b>	43.50 ± 5.41	45.55 ± 5.63	44.32 ± 6.63	46.03 ± 7.58	0.21
<b><sup>a</sup>Hexagonality</b>	44.86 ± 6.29	43.31 ± 6.05	43.59 ± 5.75	43.58 ± 7.08	0.80
<b>(%)</b>					

**Table 2:** Comparison of parameters with regard to duration of diabetes mean ± SD.

IOP: Intraocular pressure, AL: Axial length, CCT: Central corneal thickness, ACA: Anterior chamber angle, ACD: Anterior chamber depth, ACV:Anterior chamber volume, CD:endothelial cell density, CV: Variation in Size of Endothelial Cell <sup>a</sup>Kruskal-Wallis test, <sup>b</sup>Oneway ANOVA test, <sup>c</sup>Statistically significant difference.

According to glycemic statutes in diabetes, table 3 shows the results of the anterior segment parameters, IOP,corneal endothelial cell morphology, and AL measurements. There was only statistically significant difference in IOP and CD values between control and diabetic groups (under or more than 7.0% HbA1c) (p < 0.05). The mean IOP was higher in diabetic groups than control group (12.07 vs 16.87, 17.10 mmhg; p < 0.05), but there were no differences between under and more than 7.0% HbA1c in diabetic subjects (p > 0.05). The mean endothelial cell density was lower in control group than diabetic groups (2840.74 vs 2582.73, 2592.66 cell/mm<sup>2</sup>; p < 0.05); however,there were no differences between under and more than 7.0% HbA1c in diabetic patients (p > 0.05).

Parameters	Control	HbA1c	HbA1c	p-value
		< 7.0%	7.0% <	
<b>HbA1c<sup>a</sup> (%)</b>	-	6.7 ± 0.6	10.7 ± 2.4	0.0001 <sup>c</sup>
<b>IOP<sup>b</sup></b>	12.07 ± 2.18	16.87 ± 1.06	17.1 ± 1.23	0.0001 <sup>c</sup>
<b>AL<sup>b</sup></b>	22.79 ± 1.61	22.70 ± 1.30	22.86 ± 1.45	0.94
<b>CCT<sup>b</sup></b>	524.15 ± 38.59	534.25 ± 31.11	530 ± 36.1	0.39
<b>CV<sup>b</sup></b>	58.75 ± 5.03	57.73 ± 4.27	58.55 ± 4.33	0.53
<b>ACA<sup>b</sup></b>	34.73 ± 5.11	32.89 ± 7.22	33.64 ± 6.51	0.37
<b>ACD<sup>b</sup></b>	2.71 ± 0.28	2.64 ± 0.34	2.73 ± 0.33	0.32
<b>ACV<sup>a</sup></b>	145.80 ± 23.62	137.45 ± 29.82	148.64 ± 35.73	0.33
<b>Front Km<sup>a</sup></b>	43.18 ± 1.58	43.47 ± 1.61	43.53 ± 1.52	0.65
BackKm <sup>a</sup>	6.25 ± 0.28	6.25 ± 0.29	6.28 ± 0.29	0.28
<b><sup>a</sup>CD</b>	2840.7 ± 127.2	2582.7 ± 148.9	2592.6 ± 202.7	0.0001 <sup>c</sup>
<b>(cells/mm2)</b>				
<b><sup>a</sup> CV</b>	43.50 ± 5.41	45.90 ± 6.77	45.04 ± 6.25	0.14
<b><sup>a</sup>Hexagonality</b>	44.86 ± 6.29	44.00 ± 6.37	43.21 ± 6.10	0.59
<b>(%)</b>				

**Table 3:** Comparison of parameters with regard to HbA1c levels mean ± SD.

IOP: Intraocular pressure, AL: Axial length, CCT: Central corneal thickness, ACA: Anterior chamber angle, ACD: Anterior chamber depth, ACV:Anterior chamber volume, CD:endothelial cell density, CV:variation in size of endothelial cell <sup>a</sup>Kruskal-Wallis test, <sup>b</sup>Oneway ANOVA test, <sup>c</sup>Statistically significant difference.

**Discussion**

In the present study, we compared the AL, IOP, corneal endothelial cell morphology and anterior segment parameters of patients with type II DM with subjects matched by age and sex. Patients with diabetes were divided into 3 groups according to duration of the disease and also divided into 2 groups according to HbA1c levels to investigate the effects of the duration of the disease and status of glycemic control on ocular parameters. Our results suggest that there were no differences between groups in CCT, CV, ACA, ACD, AL and front Km, whereas there was a statistically significant difference in CD, back Km and IOP values.

The power of posterior cornea was significantly higher for diabetics with duration of > 10 years than in others where else there were no differences between groups in other comparison. In literature there is only one study which comments on posterior corneal power in patients with diabetes. Wiemar, *et al.* also found significantly higher optical power of the posterior corneal surface of the patients with diabetes than the healthy subjects [20]. There were no significant difference anterior corneal power between groups. Due to the little effect of posterior corneal power, chronic DM does not influence overall corneal power. Although these noteworthy results, the mechanism is unclear and further studies on posterior corneal surface in diabetic patients are needed.

In the literature, there are some studies about the effect of type II DM on corneal endothelial morphology and central corneal thickness. The previous studies that they found no differences with regard to endothelial cell density [21-24], corneal thickness [24-26], the CV of cell size [23-25] and hexagonality [23-26] between diabetes and controls; however, a few studies observed a decreased cell density [25-28], hexagonality [21,22,28] and increased the CV of cell size [21,22,26,28], corneal thickness [23]. Our study, like the others, showed a decreased cell density [23,26-28], but found no differences with regard to corneal thickness [24-26] the CV of cell size [23-25] and hexagonality [23-25] between diabetes and controls (Table 4).

Study	Diabetes/Controls(n)	CD	CV of Cell Size	Hexagonality	CCT
Schultz et al (1984)	25/23	Similiar	Increased	Decreased	None
Matsudda et al (1990)	70/30	Similiar	Increased	Decreased	None
Larsson et al(1996)	49/31	Similiar	Similiar	Similiar	Increased
Inoue et al(2002)	99/97	Decreased	Increased	Similiar	Similiar
Shenoy et al(2009)	110/110	Decreased	Increased	Decreased	None
Sundir et al(2012)	1191/120	Decreased	Similiar	Similiar	Similiar
Storr-Pausen et al(2014)	107/128	Similiar	Similiar	Similiar	Increased
Balta et al(current)	180/91	Decreased	Similiar	Similiar	Similiar

**Table 4:** Previous studies on corneal morphologic changes in patients with type II DM.

In the present study, the mean IOP was higher in diabetic patients than control group. There were no differences in IOP among diabetics with regard to the duration of the disease and the levels of HbA1c. Higher IOP levels in diabetics than healthy subjects were reported in the literature [29-31]. Briggs, *et al.* also found no difference in IOP between diabetic patients with duration of > 10 years and duration of < 10 years [32]. Latino Eye Study reported that presence of type 2 DM and longer duration of type 2 DM were associated with a higher risk of having open angle glaucoma [33]. In contrast, Rotterdam Eye Study reported that diabetes mellitus was not a risk factor for open angle glaucoma [34]. Goh, *et al.* investigated the effects of glycation end products and reported that, as a result of increased collagen cross linking in diabetic patients, stiff corneas tend to yield artificially high IOP measurements [35]. Because of the corneal hydration and swelling causes higher CCT and falsely high IOP measurements, IOP should be measured by tonometer which is least affected by corneal thickness. In the study of Kotecha, *et al.*, dynamic contour tonometer was used and IOP was measured 2 mm Hg greater than those with Goldmann applanation tonometer. There was no significant difference in IOP between diabetics and healthy subjects [36].

There are a few suggested mechanism in association between diabetes and elevated IOP. One hypothesis asserts that the hyperglycemia of aqueous humor in the eyes of diabetes patients increases the synthesis of fibronectin and cell proliferation in the trabecular meshwork, which results in increased IOP [37,38]. The other theory is that diabetes linked hyperglycemia an osmotic gradient occurs in the anterior chamber which causes excess aqueous humor. We think that there is a need to follow up diabetic patients frequently especially with high IOP as well as patients with diabetic retinopathy.

In the present study, we found no difference in AL between diabetics and healthy subjects. Uzel, *et al.* reported that boys have longer AL than girls with juvenil DM [39]. In another study He, *et al.* investigated the relationship between ocular biometry and diabetic retinopathy in adults with type 2 diabetes mellitus. They reported a negative correlation between longer AL and any diabetic retinopathy [40].

In conclusion, our study shows significant difference in CD, IOP and back Km values between diabetics and non- diabetics. Diabetes Mellitus affects the posterior corneal radius, but the overall corneal power does not change. Although further studies are needed, the diabetics with elevated IOP should be evaluated in terms of glaucoma.

### **Conflict of Interest**

No author has a financial or proprietary interest in any material or method mentioned.

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