ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.5336/ophthal.2017-56963

Corneal Endothelial and Central Corneal Thickness Changes in Patients with Uncontrolled Type II Diabetes Mellitus

Kontrolsüz Tip II Diabetes Mellituslu Hastalarda Santral Kornea Kalınlığı ve Kornea Endoteli Değişiklikleri

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Received: 15.06.2017
Received in revised form: 07.12.2017
Accepted: 12.12.2017
Available online: 24.04.2018

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ABSTRACT Objective: To compare central corneal thickness (CCT) and corneal endothelial parameters in patients with uncontrolled type II diabetes mellitus (DM) and healthy control subjects. **Material and Methods:** In this prospective comparative-observational study, we investigated right eyes of 40 patients (40 eyes) with uncontrolled type 2 DM as study group and right eyes of 43 healthy control subjects (43 eyes). Central corneal thickness (CCT) and corneal endothelial parameters including endothelial cell density (ECD), coefficient of variation of cell area (CV) and percentage of hexagonal cells were examined using non-contact specular microscopy. All obtained data were compared statistically between groups. **Results:** The study group had significantly increased mean CCT and reduced mean ECD values when compared with control group. The diabetic corneas also had higher percentage of CV in cell size and lower percentage of hexagonal cells than the control group, but the difference was not statistically significant. **Conclusion:** The CCT was increased and ECD was reduced significantly in uncontrolled type II DM patients. This study also demonstrated that study group had higher percentage of CV in cell size and had lower percentage of hexagonal cells.

Keywords: Corneal endothelium; central corneal thickness; uncontrolled type II diabetes; specular microscopy

ÖZET Amaç: Kontrolsüz tip 2 diabetes mellitus (DM) hastalarında ve sağlıklı gönüllülerde santral kornea kalınlığı (SKK) ve kornea endotel parametrelerinin karşılaştırılması. **Gereç ve Yöntemler:** Bu prospektif karşılaştırmalı-gözlemsel çalışmada kontrolsüz tip 2 DM'si olan 40 hastanın sağ gözü (40 göz) ve 43 sağlıklı gönüllünün sağ gözü (43 göz) incelendi. Santral kornea kalınlığı (SKK) ve endotel hücre yoğunluğu (EHY), hücre alanı varyasyon katsayısı ve hekzagonalite yüzdesini içeren kornea endotel parametreleri temassız speküler mikroskop ile değerlendirildi. Elde edilen veriler iki grup arasında istatistiksel olarak karşılaştırıldı. **Bulgular:** Kontrol grubu ile kıyaslandığında çalışma grubunun ortalama SKK'ı anlamlı olarak artmış, ortalama EHY'si anlamlı olarak azalmıştı. Kontrolsüz diyabetli grupta hücre alanı varyasyon katsayısı daha yüksekti ve hekzagonalite yüzdesi daha düşüktü fakat istatistiksel olarak anlamlı fark tespit edilmedi. **Sonuç:** Kontrolsüz tip 2 DM'li hastalarda SKK anlamlı olarak artmış ve EHY anlamlı olarak azalmıştır. Çalışmamızda DM'li grupta daha yüksek oranda hücre alanı varyasyon katsayısı ve daha düşük oranda hekzagonal hücre izlenmiştir.

Anahtar Kelimeler: Kornea endoteli; santral kornea kalınlığı; kontrolsüz tip 2 diyabet; speküler mikroskopi

Type II diabetes mellitus (DM) has become worldwide epidemic. By 2025, it is estimated that global prevalence will be approximately 380 million for type 2 DM.[1,2] It is a chronic metabolic disease characterized by hyperglycaemia and affects the corneal epithelium, epithelial basement membrane complexes, stroma and endothelial cells.[3-5]

Investigators showed that diabetes causes corneal morphology and endothelium abnormalities and it may cause physiological instability in

cornea.[4-6] As a result of diabetic corneal morphological and endothelial changes; corneal pathologies such as persistent epithelial erosions, superficial punctate keratitis, epithelial edema, reduced corneal sensitivity, neurotrophic ulcers have been reported.[7,8] Moreover, diabetes make the cornea more fragile and risky for ocular surgery.[9,10]

The aim of this study is to compare the central corneal thickness (CCT) and corneal endothelial parameters in patients with uncontrolled type II DM and healthy subjects using noncontact specular microscope. To best of our knowledge, there are only a few reports about corneal endothelial parameters in patients with uncontrolled type II DM in literature.

MATERIAL AND METHODS

SUBJECTS

This prospective observational, cross-sectional study included 83 eyes of 83 Caucasians who were examined at the Department of Ophthalmology, Gaziantep University Hospital from August 2016 to May 2017. It was approved by local ethics committee and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from each participant.

The study group included 40 eyes of 40 patients who were diagnosed with uncontrolled type II DM and glycosylated HbA1c levels were over 7.9% for 12 months.[11,12] The diagnosis of type II DM was based on criteria of the World Health Organisation (WHO). Control group included 43 eyes of 43 participants who did not have any eye and systemic disease. All participitants underwent complete ocular examination and detailed medical history was obtained from each participant. Exclusion criteria were active or previous eye infection or inflammation, glaucoma, previous ocular surgery, previous ocular trauma, previous retinal laser photocoagulation, active or previous corneal disease, eyelid disorders, contact lens wear and regular usage of topical ocular medications or known systemic drugs. Patient demographics and clinical characteristics including age, gender, duration of type II DM, most recent glycosylated HbA1c value, status of retina and current medical treatment for DM were recorded.

MEASUREMENT TECHNIQUE

The CEM-530 (Nidek Co, Ltd, Gamagori, Japan) non-contact specular microscope was used for all measurements. Patients were asked to blink just before measurements and all measurements were taken by an experienced examiner. Only right eye of each patient was measured. For each patient 3 consecutive measurements were performed and mean value of CCT, corneal endothelial cell density (ECD) (cells/mm^2), coefficient of variation of the cell area (CV, %) and cell hexagonality (proportion of hexagonal cells in percentage, %) were recorded.

STATISTICAL ANALYZES

The SPSS 16.0 software for Windows (SPSS Inc, Chicago, IL) was used to analyze results. Outcomes were given as mean ± standard deviation. Age and gender distribution between groups were compared using Chi-square test. CCT, ECD, (cells/mm^2), CV, (%) and cell hexagonality (proportion of hexagonal cells in percentage, %) were compared between groups using independent sample t-test. P value less than 0.05 was considered significant.

RESULTS

The study group included 40 eyes of 40 patients who were diagnosed with uncontrolled type II DM (HbA1c ≥8.0 for 12 months). Control group included 43 eyes of 43 healthy participants. The patient demographics, duration of diabetes, status of diabetic retinopathy, glycosylated HbA1c levels and regulatory therapy of patients were summarized in Table 1. There was no significant difference between groups regarding the age and gender (p=0.671, p=0.872; respectively).

The mean values of corneal parameters including CCT, ECD, CV and cell hexagonality (proportion of hexagonal cells in percentage, %) were shown in Table 2.

The study group had significantly increased CCT and decreased ECD when compared with

TABLE 1: Demographics and clinical characteristics of patients.

	Study Group 40 eyes, (%)	Control Group 43 eyes, (%)	P value
Age, years			
Mean±SD	56.3±7.8	55.4±9.5	**0.671***
Range	(40-70)	(40-72)	
Gender			
Male	18 (45%)	20 (46.5%)	**0.872***
Female	22 (55%)	23 (53.5%)	
Duration of type II diabetes mellitus, years			
Mean±SD	10.9±3.3	-	
Range	(5-20)	-	
Status of diabetic retinopathy			
BDR	9 (22.5%)	-	
NPDR	24 (60%)	-	
PDR	7 (17.5%)	-	
HbA1c , %			
Mean±SD	10.8±1.5	-	
Range	(8.0-13.5)	-	
Regulatory therapy of diabetes mellitus			
Oral antidiabetic drugs	10 (25%)	-	
Insulin therapy	30 (75%)	-	

SD: Standard deviation, BDR: Background Diabetic retinopathy, NPDR: Nonproliferative DR, PDR: Proliferative DR, HbA1c: Glycosylated hemoglobin.
* Chi-square test was used.

TABLO 2: Central corneal thickness and corneal endothelial parameters.

Corneal parameters	Study group	Control grup	P value
CCT, µm			
Mean±SD	560.3±30.1	543.2 ± 35.3	0.030*
Range	(505-620)	(490-616)	
ECD, cell/mm^2			
Mean±SD	2460.5± 224.5	2606.8±222.9	0.007*
Range	(2082-2873)	(2167-3042)	
CV, %			
Mean±SD	33.3±4.8	31.2±4.4	0.064*
Range	(26-45)	(23-40)	
Hexoganality, %			
Mean±SD	60.0 ±6.1	61.5±5.0	0.235*
Range	(30-62)	(45-65)	

Abbreviations: SD: Standard deviation; **CCT:** Central corneal thickness; **ECD:** Endothelial cell density; **CV:** Coefficient of variation of cell area. *Independent sample t-test was used.

control group (p=0.030, p=0.007; respectively). We also showed that study group had higher percentage of CV in cell size and had lower percentage of hexagonal cells. There was no significant difference between groups regarding the mean values of CV and cell hexagonality (p=0.064, p=0.235; respectively).

DISCUSSION

Corneal morphological and endothelial changes in diabetic patients have been evaluated in previous studies.[1-10,13,14] Majority of these reports showed that diabetic corneas were thicker when compared to non-diabetic healthy eyes.[5-7,14-16] Investigators demonstrated that endothelial pump dysfunction due to hyperglycaemia has been shown as the main mechanism of increased CCT.[6,15,17] Lee et al. have reported that CCT increased significantly with the duration of DM.[5] Association between HbA1c and CCT is controversial issue. Zengin et al. showed that patients with higher HbA1c levels (≥ 7%) had thicker corneas than the patients with lower HbA1c levels (<7%).[16] In contrast, some authors reported no significant difference in CCT when compared diabetic and non-diabetic eyes.[14-19] In our study, we showed that CCT of patients

who had uncontrolled type II DM for over 5 years and HbA1c levels were over 7.9% for minimum 12 months; were significantly higher than non-diabetic healthy eyes. Some authors showed that there is no correlation between duration of DM and CCT.[14,15] In contrast, some authors reported that no any association between HbA1c levels and CCT.[14,19] We observed that patients with uncontrolled type II DM for a year has increased CCT when compared with CCT of healthy subjects.

The main role of corneal endothelial cells is to provide corneal transparency. Some factors such as age, contact lens wear, intraocular surgery and DM may affect the health of cornea endothelial cells.[20,21] Non-contact specular microscopy, which provides computer-assisted cell density determination and morphometric analysis of corneal endothelium, is a very useful method for monitoring health of endothelial cells. ECD, CV and the percentage of hexagonal cells are important parameters for monitoring corneal endothelium health.[22] Majority of previous reports have demonstrated that diabetes mellitus may cause decrease in ECD and percentage of hexagonal cells (polymorphism), as well as increase in CV (polymegathism).[5,13,23] Our outcomes were similar to the previous reports. The mean ECD was reduced significantly (approximately %5.6) in uncontrolled type 2 DM patients when compared with control group values (p=0.007). Additionally, we observed increased CV and decreased hexagonality values when compared with control group. However, there was no statistically significant difference between groups regarding CV and hexagonality. Our coefficient of variation in of cell area values was similar to previous reports of Sudhir et al. and Chen et al. but not accordance with the outcomes of Lee et al. Shenoy et al. and El-Agamy et al. We also demonstrated no significant difference in the percentage of hexagonal cells between the uncontrolled type II diabetic patients and the healthy controls, which was in accordance with the outcomes of Storr-Paulsen et al. El-Agamy et al. Inoue et al. and Sudhir et al. In contrast, not similar to outcomes of Choo et al. and Lee et al. We thought that differences of outcomes of previous reports especially in CV and hexagonality values are related some factors.[1,5,7,5,13,23-25] First of all; non-homogeneous study groups is an important factor. Duration of diabetes, metabolic control status of patients, age groups and regulatory therapy of patients may cause different outcomes. Secondly, non-contact specular microscopy measurement methods and analysis software may show differences between devices.[22,26]

Our results demonstrated that uncontrolled type II DM causes statistically significant decrease in ECD and statistically significant increase in CCT when controlled with healthy subjects. Investigators showed that high glucose levels lead to increased activity of aldose reductase.[1-9] As a result of increased activation of sorbitol-aldose reductase pathway; sorbitol is over produced and it is an osmotic agent which causes swelling of endothelial cells. Other unfavourable effect of DM on endothelial cells is reducing activity of Na^+-K^+ ATPase pump. It causes permeability, metabolic and morphologic changes in endothelial cells, which leads to decreased ATP energy production of endothelial cells. All these adverse metabolic morphologic and permeability changes causes disruption in corneal endothelial cell activities and cornea.[13-21]

CONCLUSION

In summary, our study demonstrated that uncontrolled type II DM causes significantly increased CCT and decreased ECD. Hexagonality and CV values did not significantly differ between groups. Our inclusion and exclusion criteria produced a relatively small group for this study. Therefore, large population based studies are needed for certain results for hexagonality and CV in uncontrolled type II DM patients.

Acknowledgments

The authors have no financial interest in any of the equipment used. No financial assistance was received for this study.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct

connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Alper Mete, Sabit Kimyon;* ***Design:*** *Alper Mete, Sabit Kimyon;* ***Control/Supervision:*** *Alper Mete, Sabit Kimyon;* ***Data Collection and/or Processing:*** *Seda Çeri Ömer Koyuncu;* ***Analysis and/or Interpretation:*** *Alper Mete, Sabit Kimyon;* ***Literature Review:*** *Alper Mete, Sabit Kimyon;* ***Writing the Article:*** *Alper Mete, Sabit Kimyon;* ***Critical Review:*** *Alper Mete, Sabit Kimyon.*

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