Evaluation of Central Corneal Epithelial Thickness With Anterior Segment OCT in Patients With Type 2 Diabetes Mellitus

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Abstract

Aim: The aim of this study was to evaluate the central corneal thickness (CCT) and central corneal epithelial thickness (CCET) in patients with Type 2 diabetes mellitus (DM), and the effect of the duration of diabetes, the degree of diabetic retinopathy (DR), and HbA1c level.

Method: CCT and CCET values of 72 patients diagnosed with type 2 DM and 72 healthy individuals were measured by anterior segment optical coherence tomography (AS-OCT). The eye tear function was evaluated with the Tear Break-up Time test (TBUT) and the Schirmer test. From the results of fundus examination, the diabetic patients were grouped as those without DR, with non-proliferative DR, and with proliferative DR. The disease duration and the HbA1c levels were recorded.

Results: In the diabetic patients, the mean CCT was determined to be thicker ($p=0.025$), the CCET was thinner ($p=0.003$), and the TBUT and Schirmer values were lower ($p<0.001$, $p<0.001$, respectively). The duration of diabetes and the HbA1c level were not found to have any statistically significant effect on these parameters ($p>0.05$). The presence of retinopathy had no significant effect on CCT, TBUT and Schirmer values. The CCET was determined to be thinner in patients with retinopathy ($p<0.001$).

Conclusion: As the corneal epithelial thickness is reduced in patients with advanced diabetic retinopathy, corneal epithelial pathologies can be seen more often. Therefore, early and effective treatment can be started taking into consideration the complications which may develop associated with the corneal epithelium following surgical procedures, especially those applied to the cornea.

Introduction

Diabetes mellitus is a systemic metabolic disease which is seen with chronic hyperglycemia, and prevalence of this disease is currently increasing. Although diabetic retinopathy, nephropathy, and neuropathy are the most commonly seen complications, almost all tissues and organs are affected.¹ These complications are related to the duration of diabetes and poor metabolic control (high HbA1c level).^{2,3} As one of the most common complications of DM, diabetic retinopathy is one of the leading causes of blindness in developed countries.⁴ Other than the retina, diabetes also causes dry eye by affecting the cornea, conjunctiva and lacrimal glands, and anterior segment pathologies such as punctate epithelial keratopathy, recurrent corneal erosion, persistent epithelial defect, and endothelial damage.⁵⁻⁸

Diabetic keratopathy affects approximately 70% of DM patients and is generally subclinical.⁹ An effect on the cornea in particular affects the sight and quality of life of the patient, and complications associated with surgical procedures (intraocular surgery, refractive surgery) are increased.¹⁰ Therefore, recent studies have focussed on the effect of diabetes on the anterior segment. Developments in the technology of ocular surface imaging have enabled the microstructural effect of diabetes on the anterior segment to be more clearly seen. Both the more frequent occurrence of dry eye, and reduced epithelial

regeneration as a result of reduced corneal innervation may have a negative effect on the corneal epithelium in diabetic patients.

According to our literature review, our study is the first to evaluate the CCET with AS-OCT in patients with type 2 DM. The aim of this study was to evaluate the effect of duration of diabetes, HbA1c level and degree of diabetic retinopathy on CCT and CCET in patients with type 2 DM.

Material-method

This prospective clinical study was approved by the Human Research Ethics Committee and was conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all the study participants.

The study included 72 eyes of 72 patients diagnosed with Type 2 DM who presented at the Ophthalmology Polyclinic between March 2020 and January 2021. A control group was formed of 72 healthy individuals without diabetes. Only the right eyes of the patients were included for evaluation. Study exclusion criteria were defined as a history of ocular surgery, trauma history, the presence of corneal pathology, contact lens use, the presence of retinopathy other than diabetic retinopathy, other eye pathologies such as glaucoma or uveitis, high refractive error (3 diopter cylindrical, 6 diopter spherical), or the application of retinal photocoagulation within the last 3 months.

A record was made for each patient of demographic characteristics (age, gender), the duration of diabetes, and HbA1c level examined within the previous week. Each patient then underwent a full ophthalmological examination. Best corrected visual acuity (BCVA) was assessed with a Snellen chart and recorded. Biomicroscopic examination was made of the anterior segment. With the consideration that corneal thickness could be affected by invasive procedures such as Goldmann applanation tonometry, AS-OCT was performed first. The central corneal thickness (CCT) and central corneal epithelial thickness (CCET) were evaluated with Spectral Domain anterior segment optical coherence tomography (AS-OCT) (OCT HS100, Canon, Australia). The mean CCT and CCET of the central 5mm was evaluated.

Dry eye was evaluated with the Tear Break-Up Time (TBUT) and Schirmer 2 tests. For the TBUT test, 2% fluorescein drops were dropped into the eye. The time was recorded from the last blink to the time the first dry point was seen; this procedure was repeated and the average value was taken for analysis. For the Schirmer 2 test, local anaesthetic drops were dropped into the eye and a Schirmer strip was placed on the lower fornix. By measuring the wetness on the strip after 5 mins, the aqueous tear secretion was determined. After pupil dilatation, the degree of retinopathy was determined in all the diabetic patients. The patients were classified in 3 groups according to the Early Treatment Diabetic Retinopathy Study as those with no diabetic retinopathy (NDR), those with non-proliferative diabetic retinopathy (NPDR) and those with proliferative diabetic retinopathy (PDR). ¹¹

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS vn. 16.0 software. Conformity of numerical variables to normal distribution was assessed with the Kolmogorov-Smirnov test. The descriptive statistics of variables with normal distribution such as CCT and CCET were stated as mean±standard deviation values, and those not showing normal distribution as median (minimum-maximum) values. Variables with normal distribution were compared using the Student's t-test. Variance analysis was performed with ANOVA and post-hoc analyses with Bonferroni correction. Variables not showing normal distribution such as TBUT and Schirmer values were compared using the Mann Whitney U-test. Variance analysis was applied with the Kruskal Wallis test, and subgroup comparisons with the Bonferroni corrected Mann Whitney U-test. Categorical variables were stated as number (n) and percentage (%), and were compared with the Chi-square test. A value of $p<0.05$ was accepted as statistically significant.

Results

Evaluation was made of 72 eyes of 72 patients with Type 2 diabetes mellitus and a control group of 72 healthy subjects. The patient group comprised 43 females and 29 males with a mean age of 57.85 ± 7.83 years and the control group comprised 42 females and 30 males with a mean age of 58.83 ± 9.77 years. No statistically significant difference was found between the groups in respect of age and gender ($p=0.505$, $p=0.500$, respectively). In the diabetic group, disease duration was mean 12.90 ± 7.51 years and mean HbA1c level was 9.01 ± 1.88 . Of the 72 patients in the diabetic group, 34 (47.22%) had no diabetic retinopathy (NDR), and diabetic retinopathy was determined in 38 (52.78%) as 17 (23.61%) patients with NPDR and 21 (29.17%) with PDR.

In the diabetic patients, the mean CCT was determined to be thicker ($p=0.025$), the CCET was thinner ($p=0.003$), and the TBUT and Schirmer values were lower ($p<0.001$, $p<0.001$, respectively) compared to the control group (Table 1).

Table 1
The CCT, CCET, TBUT and Schirmer values of the diabetic patient group and the control group

	Diabetic group (n=72)	Control group (n=72)	P value
CCT μm (mean±sd)	544.33±31.20	533.77±24.45	$p=0.025^*$
CCET μm (mean±sd)	52.25±3.61	53.95±3.05	$p=0.003^*$
TBUT sec [median(min-max)]	5 (1-20)	10 (3-28)	$p<0.001^*$
Schirmer mm [median(min-max)]	8 (1-25)	15 (3-25)	$p<0.001^*$
CCT: Central Corneal Thickness, CCET: Central Corneal Epithelial Thickness, TBUT: Tear Break Up Time			
* $p<0.05$			

The effects of the duration of diabetes, the HbA1c level, and the degree of DR on CCT, CCET, TBUT, and Schirmer values are shown in Tables 2, 3, and 4. The duration of diabetes and the HbA1c level were not found to have any statistically significant effect on these parameters ($p>0.05$). The presence of retinopathy had no significant effect on CCT, TBUT and Schirmer values ($p>0.05$). The CCET was determined to be thinner in patients with retinopathy ($p<0.001$).

Table 2
The effect of the HbA1c level on CCT, CCET, TBUT and Schirmer

	HbA1c ≤ 8.5 (n=34)	HbA1c > 8.5 (n=38)	P value
CCT μm (mean $\pm$ sd)	538.08 $\pm$ 29.05	549.92 $\pm$ 32.37	p=0.109
CCET μm (mean $\pm$ sd)	52.53 $\pm$ 3.89	52.00 $\pm$ 3.38	p=0.539
TBUT sec [median(min-max)]	5 (1-20)	4 (1-15)	p=0.071
Schirmer mm [median(min-max)]	9 (1-25)	8 (2-20)	p=0.233
CCT: Central Corneal Thickness, CCET: Central Corneal Epithelial Thickness, TBUT: Tear Break Up Time			

Table 3
The effect of the duration of diabetes on CCT, CCET, TBUT and Schirmer

	≤ 15 years (n=41)	> 15 years (n=31)	P value
CCT μm (mean $\pm$ sd)	539.02 $\pm$ 29.53	551.35 $\pm$ 32.44	p=0.097
CCET μm (mean $\pm$ sd)	51.83 $\pm$ 3.35	52.81 $\pm$ 3.92	p=0.259
TBUT sec [median(min-max)]	5 (1-20)	4 (2-11)	p=0.077
Schirmer mm [median(min-max)]	8 (1-25)	9 (2-20)	p=0.209
CCT: Central Corneal Thickness, CCET: Central Corneal Epithelial Thickness, TBUT: Tear Break Up Time			

Table 4
The effect of the presence of diabetic retinopathy on CCT, CCET, TBUT and Schirmer

	DR absent (n=34)	DR present (n=38)	P value
CCT μm (mean $\pm$ sd)	546.29 $\pm$ 28.38	542.58 $\pm$ 33.81	p=1.000
CCET μm (mean $\pm$ sd)	53.79 $\pm$ 3.09	50.87 $\pm$ 3.52	p<0.001*
TBUT sec [median(min-max)]	5.5 (2-20)	4 (1-18)	p=0.103
Schirmer mm [median(min-max)]	9 (2-25)	8 (1-20)	P=0.419
CCT: Central Corneal Thickness, CCET: Central Corneal Epithelial Thickness, TBUT: Tear Break Up Time, DR: Diabetic Retinopathy			
*p<0.05			

Subgroup analysis was performed to evaluate the effect of the degree of diabetic retinopathy on CCET. No significant difference was determined between the control group and the NDR group in respect of CCET (p=1.000). A statistically significant difference was determined between the control group and the NPDR and PDR groups (p=0.047, p<0.001, respectively).

Discussion

With recent developments in technology, the effect of diabetes on the anterior segment can now be evaluated objectively. Within the anterior segment structures, the cornea has the greatest effect on sight prognosis. Direct damage to corneal cells (epithelium, stroma, endothelium), reduced corneal innervation, and impaired ocular surface homeostasis associated with dry eye, cause corneal pathologies. Impaired proliferation, migration, and adhesion of the corneal epithelium in particular leads to recurrent corneal erosions and persistent epithelial defects. All of these render the cornea more sensitive to minor trauma and pathogens.¹²

Dry eye and ocular surface inflammation are often seen in diabetes, with consequent changes in tear production, stability and the quality of the lipid layer. Both microvascular damage of the lacrimal gland and reduced sensory innervation of the lacrimal gland as a result of neuropathy cause a reduction in tear secretion and a deficiency of aqueous tears.⁷ A decreased number of goblet cells in the conjunctiva affects tear stability by decreasing mucin secretion.^{7,13} In addition, meibomian gland dysfunction, which is often seen in diabetic patients, causes deficiencies in the lipid layer and increases the evaporation of tears.^{14,15} Therefore, as each of the layers of tears is affected in diabetic patients, dry eye is seen more frequently. In the current study, the values of the Schirmer test, which evaluates tear secretion, and of the TBUT test, which evaluates tear stability, were determined to be lower in the diabetic patients than in the control group. However, no relationship was found with the duration of diabetes, the degree of DR, or the HbA1c level.

Corneal stromal hydration is kept in balance with the endothelial pump function and the epithelial barrier function. Chronic metabolic stress caused by hyperglycemia in the corneal epithelium, stroma and endothelium affects corneal thickness.¹⁶ A reduction in the number of endothelial cells and impaired function especially cause an increase in CCT.¹⁷ Conflicting results have been obtained in studies that have evaluated corneal thickness in diabetic patients. While some studies have shown that the CCT is thicker in diabetic patients than control subjects.^{17–19} others have reported no significant difference.^{20–23} This difference between studies may be due to the difference in the time of measurement and the device used, the metabolic status of the patient at the time of measurement, the duration of diabetes, the severity of retinopathy, and different ethnic origins. The results of the current study showed that the CCT was statistically significantly thicker in the diabetic patients than in the control group. The duration of diabetes, HbA1c level, and DR degree were not determined to have a significant effect on CCT. However, when the NDR, NPDR, and PDR groups were compared separately with the control group, the difference between them was seen to gradually decrease ($p=0.205$, $p=0.535$, $p=1.00$). As will be explained below, this was thought to be associated with the CCET decreasing as the DR degree increased.

The corneal epithelium is kept in continuous balance with limbal stem cell proliferation and migration corresponding to the loss of surface cells. To be able to maintain the integrity of the corneal epithelium, in addition to a healthy tear layer, healthy nerve innervation is necessary. Various neurotrophic factors that are expressed provide proliferation and differentiation of stem cells in the limbus. As a result of neuropathy developing in diabetic patients, a reduction in these neurotrophic factors causes epithelial fragility, recurrent corneal erosions and persistent epithelial defects.²⁴ Several studies have shown that the sub-basal nerve plexus (SBNP) is clearly affected in diabetic patients (a reduction in the number and length of nerve fibres, decreased branching, increased tortuosity).^{25–27} Basal epithelial cell density (BECD) and epithelial thickness decrease together with the development of corneal neuropathy.^{25, 26, 28} These changes in the SBNP have been found to be related to peripheral neuropathy and diabetic retinopathy.^{28–30} Rosenberg et al showed that the corneal epithelium was significantly thinner in patients with severe neuropathy compared to patients without neuropathy.²⁵ Nitoda et al reported that corneal neuropathy was related to peripheral neuropathy and the degree of DR,²⁹ while Chang et al found that BECD was reduced together with DR, and this was in parallel to SBNP loss.³⁰ However, different results have been obtained in studies that have evaluated the effect of HbA1c level and the duration of diabetes on SBNP. Pellegrini et al showed that both parameters had an effect on changes in the SBNP,³¹ while Kallinikos et al reported that there was no significant effect.³² Lomoriello et al suggested that there was an inverse correlation with the duration of diabetes and the HbA1c level had no significant effect³³ while in contrast, Dehghani et al suggested that there was an inverse correlation with the HbA1c level, and there was no significant effect of the duration of diabetes.

In the current study, the CCET was determined to be statistically significantly thinner in the diabetic group compared to the control group. Although this decrease was not related to the duration of diabetes and HbA1c level, there was seen to be an inverse correlation with the degree of diabetic retinopathy. No

significant difference was determined between the control group and the group without DR, and there was a significant difference between the control group and the patients with DR. As the degree of DR increased, so the CCET decreased. This showed that the difference between the control group and the diabetic group was due to the patients with retinopathy.

There may be 3 reasons for the decrease in CCET in diabetes: i) secondary to dry eye, which is common in diabetic patients, ii) impaired epithelial homeostasis associated with corneal neuropathy, and iii) the effect of retinal photocoagulation (RP). There has been a recent increase in studies evaluating the effect of dry eye on the corneal epithelium. Trauma occurring when blinking associated with reduced lubrication in dry eye, impaired feeding of the epithelial cells, and an increase in inflammation, affect the corneal epithelium. Some studies have shown that the epithelium is thinner in patients with dry eye,^{35–38} some that there is no change,³⁹ and some that it has even increased.^{40,41} As dry eye is frequently seen in diabetic patients, it may be a factor in the decrease in CCET. In the current study, although dry eye was seen more often in diabetic patients, no significant difference was determined between those with and without DR. Therefore, as the severity of dry eye does not increase with the severity of DR, even if there is a partial effect, this was not thought to be the main reason. There are studies in literature showing that by increasing corneal neuropathy, RP reduced epithelial thickness,³⁰ or had no effect.⁴² As RP had been applied to all the current study patients with PDR, the NPDR and PDR groups were compared and no significant difference was determined. The main reason for the decrease in CCET was thought to be the increase in the degree of corneal neuropathy together with the DR degree, as has been shown in previous studies. That CCET was not found to be correlated with the duration of diabetes and the HbA1c level suggested that these parameters had no effect on the development of corneal neuropathy, as reported by Kallinikos et al. This is perhaps because of the low reliability of HbA1c level and diabetes duration data in evaluating the long-term effect of diabetes on the eye. Because the HbA1c level is a cross-sectional measurement, it only provides information about blood glucose levels in the last 3 months and may not show long-term metabolic control. Since the duration of diabetes is determined based on the patient's statement, it may not reflect the actual duration. Therefore, the degree of diabetic retinopathy provides us with more objective information.

In conclusion, the epithelial layer is the first part of the cornea to be exposed to environmental factors and has an important place in ensuring corneal integrity. Corneal epithelial pathologies may be seen more frequently in patients with advanced diabetic retinopathy due to reduced corneal epithelial thickness. Early and effective treatment should be initiated in these patients, as epithelial defects that occur after simple trauma or surgery may cause greater problems.

Declarations

Conflict of interest:

There is no conflict of interest

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