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Does central corneal thickness correlate with haemoglobin A1c level and disease severity in diabetes type II?

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Aim: To compare central corneal thickness (CCT) values of patients with type II diabetes mellitus with those of healthy subjects, and evaluate the effect of disease duration, retinopathy severity, and HbA1c level on CCT.

Materials and methods: One hundred and twenty-six consecutive type II diabetic patients and 36 non-diabetic healthy subjects were included in the study. CCT was measured using the Orbscan II corneal topography system. The effect of disease duration, retinopathy severity, and HbA1c level on CCT was evaluated using analysis of variance (ANOVA) and the independent sample t test.

Results: CCT was significantly higher in diabetic patients than in non-diabetic subjects. Severity of retinopathy and disease duration had no apparent effect on CCT. Diabetic patients with HbA1c levels over 7% had thicker corneas than patients with HbA1c levels under 7% (P = 0.021).

Conclusion: Type II diabetic patients have thicker corneas than non-diabetic subjects. Higher HBA1c level may be a marker for predicting the increase in CCT in patients with type II diabetes.

Key words: Central corneal thickness, diabetes, disease duration, disease severity

Tip II diabetli hastalarda hastalığın şiddeti ve hemoglobin A1c seviyesi santral kornea kalınlığı ile ilişkili midir?

Amaç: Bu çalışmada tip II diyabetes mellituslu hastalarda santral kornea kalınlığını (SKK) sağlıklı bireylerle karşılaştırmak ve hastalık süresinin, retinopati şiddetinin ve HbA1c düzeyinin SKK üzerine etkisini incelemek amaçlanmıştır.

Yöntem ve gereç: Tip II diyabetli 126 hasta ve diyabeti olmayan sağlıklı 36 olgu çalışmaya dahil edilmiştir. SKK Orbscan II korneal topografi cihazı ile ölçülmüştür. Hastalığın süresi, retinopati şiddeti ve HbA1c düzeyinin SKK üzerine etkisi varyans analizi (ANOVA) ve bağımsız değişken t testi ile değerlendirilmiştir.

Bulgular: SKK, tip II diyabetik hastalarda diyabeti olmayanlara göre istatistiksel olarak anlamlı yüksek bulunmuştur. Retinopati şiddetinin ve hastalık süresinin SKK üzerine belirgin bir etkisi saptanmamıştır. HbA1c düzeyi % 7'nin üzerinde olan tip II diyabetik hastalarda, HbA1c düzeyi % 7'nin altında olanlara göre SKK daha fazla saptanmıştır (P = 0,021).

Sonuç: Tip II diyabetli hastalar diyabetik olmayanlara göre daha kalın korneaya sahiptirler. Yüksek HbA1c düzeyi tip II diyabetli hastalarda artmış SKK için belirleyici bir faktör olabilir.

Anahtar sözcükler: Santral kornea kalınlığı, diyabet, hastalık süresi, hastalık şiddeti

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Introduction

Diabetes mellitus (DM) is a systemic disease that alters the major metabolic pathway in the human body and destroys major organ systems. Diabetic retinopathy is the most common and investigated ocular complication. However, morphologic and functional changes in the cornea have been studied less frequently in diabetic eyes (1-7). Stromal and subbasal nerve abnormalities (1), low endothelial cell density and hexagonality (2), reduction in corneal sensitivity (3), increased corneal autofluorescence (4), and recurrent corneal erosions (5) are among the corneal changes observed in diabetic patients. Corneal thickness has also been evaluated in previous studies (2,3,6,8,9). However, to the best of our knowledge, the effects of HbA1c level on central corneal thickness (CCT) have not so far been studied.

In this prospective study, the CCT of patients with type II DM was compared with that of healthy subjects. The correlations of CCT with duration of diabetes, severity of diabetic retinopathy, and HbA1c level were analysed.

Materials and methods

Our study population comprised 126 consecutive type II diabetic patients and 36 non-diabetic healthy subjects. All study subjects underwent a routine ophthalmologic examination. Patients who had had previous intraocular surgery, ocular trauma, intraocular inflammation, and glaucoma, and who wore contact lenses were excluded. Those who had received laser photocoagulation within less than 1 month were also excluded. CCT was measured using the Orbscan II corneal topography system (Bausch & Lomb, Rochester, NY, USA). Keratometry readings and refraction values were obtained with an auto refract-keratometer (Nikon, NRK-8000, Japan) 30 min after the instillation of 1% cyclopentolate (Siklоplejin, Abdi İbrahim, İstanbul, Turkey) and 0.5% tropicamide (Tropamid, Bilim, İstanbul, Turkey). Three consecutive measurements were taken with the Orbscan II and the auto refract-keratometer. The results of 3 readings were averaged. The steepest and flattest keratometric values were recorded. Spherical equivalent was calculated with regard to refraction. Diabetic patients were classified according to diabetes duration (longer or shorter than 10 years) and HbA1c levels (over or under 7%). The HbA1c values were obtained within 1 week of the CCT measurement.

Retinopathy status was evaluated by indirect ophthalmoscopy following pupillary dilation and Goldmann 3 mirror examination at the slit-lamp. Patients were classified according to retinopathy stage. The first group included 31 patients having diabetes but no retinopathy, the second group included 30 patients having mild to moderate nonproliferative retinopathy, the third group included 34 patients having severe nonproliferative retinopathy, the fourth group included 31 patients having proliferative retinopathy, and the fifth group included 36 age-matched non-diabetic control subjects. All measurements were performed at the same time in the afternoon.

Measurements of the right eye were used for analysis. Statistical analysis was performed using analysis of variance (ANOVA) and the independent sample t test in SPSS version 11.0 (SPSS, Chicago, IL, USA).

Results

Clinical features of the study population are shown in Table 1. No statistically significant difference was noted in age distribution among the groups ($P = 0.353$, ANOVA). Mean duration of diabetes was 12.4 ± 7.5 years (range 1-30 years). Central corneal thickness measurements are shown in Table 1 and the Figure. The central cornea was significantly thinner in the control group when compared to all 4 diabetic groups ($P < 0.001$, ANOVA) (Table 2). In diabetic eyes, the central cornea was thicker in eyes in the mild to moderate nonproliferative retinopathy group when compared to those in the no retinopathy group ($P = 0.034$). When diabetic patients were analysed in terms of disease duration and compared with each other, CCT was similar in patients that had had diabetes for less than 10 years and longer than 10 years ($P = 0.522$) (Table 3). When the patients were analysed in terms of HbA1c levels, patients with HbA1c levels over 7% had thicker corneas than the patients with HbA1c levels under 7% (Table 4).

Table 1. Clinical data of the study population.

	Control	No retinopathy	Mild to moderate nonproliferative retinopathy	Severe nonproliferative retinopathy	Proliferative retinopathy
Subjects (n)	36	31	30	34	31
Mean Age (Years)* (Range)	54.58 ± 8.98 (36-70)	54.35 ± 8.87 (42-77)	56.73 ± 7.95 (42-76)	56.91 ± 9.23 (39-73)	58.03 ± 7.58 (41-72)
Sex (Male/Female)	19/17	15/16	11/19	15/19	12/19
CCT (µm)	537.11 ± 31.82	555.03 ± 31.49	574.86 ± 39.69	568.29 ± 40.05	556.62 ± 36.70
K (steep axis) (D)	43.09 ± 1.12	43.94 ± 1.64	43.32 ± 3.82	43.57 ± 1.17	43.77 ± 1.45
K (flat axis) (D)	42.77 ± 1.12	43.35 ± 1.5	43.31 ± 1.4	43.11 ± 1.21	43.16 ± 1.5
SE (D)	-0.01 ± 1.15	0.17 ± 1.07	0.29 ± 1.50	0.56 ± 0.90	0.18 ± 1.32

K, mean keratometry reading; D, diopter; SE, mean spherical equivalent
* Mean age of the groups are similar (P = 0.353, ANOVA)

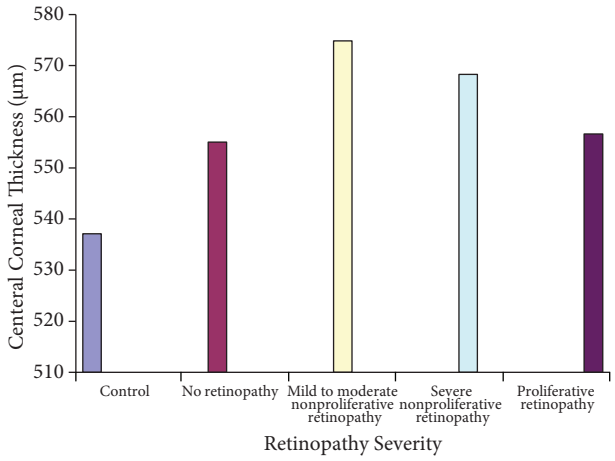

Figure 1. Mean corneal thickness values in the study sub-groups classified according to retinopathy severity.

When mean steep keratometric values in each subgroup were compared with each other, there was no statistically significant difference among the groups (P = 0.469, ANOVA) (Table 1). Mean flat keratometric values in each subgroup were also similar (P = 0.423, ANOVA). There was also no difference among the groups according to spherical equivalent (P = 0.432, ANOVA) (Table 1).

Discussion

Several studies have evaluated corneal thickness in diabetic eyes (2,3,6,8-11) (Table 5). Most studies and the current study showed that diabetic eyes had increased CCT when compared to non-diabetic eyes (2,6,8,9). Some studies (3,8,10) included only type I diabetics and some investigated both type I and II diabetics (2,6,9,11). Patients with type II diabetics were studied and it was found that type II diabetics even without retinopathy had thicker central corneas than non-diabetic subjects. In contrast to the results obtained in the present study, Larsson et al. (6) and Schultz et al. (11) did not find any increase in CCT in type II diabetics when compared to age-matched controls.

Why does corneal thickness increase in diabetic eyes? Although the cause is obscure, it is postulated that endothelial pump function disturbance due to reduction of Na^+/K^+ ATPase activity results in and increase in stromal hydration (8,9,12). The central cornea might get thicker following intraocular surgery even in patients without diabetic retinopathy. Sometimes corneal oedema may persist following intraocular surgery in diabetic eyes (13). Therefore, assessing CCT in diabetic patients before any surgery

Table 2. Comparative results of CCT among the study groups according to retinopathy severity ¶(P values).

	Control	No retinopathy	Mild to moderate nonproliferative retinopathy	Severe nonproliferative retinopathy	Proliferative retinopathy
Control	_	0.028*	<0.001*	<0.001*	0.030*
No retinopathy	0.028*	_	0.034	0.145	0.855
Mild to moderate nonproliferative retinopathy	<0.001*	0.034	_	0.513	0.067
Severe nonproliferative retinopathy	<0.001*	0.145	0.513	_	0.227
Proliferative retinopathy	0.030*	0.855	0.067	0.227	_

¶ *P*<0.001 (When comparing the groups together with ANOVA)
* Statistically significant (independent sample t test)

Table 3. CCT of the diabetic patients according to duration of diabetes.

Duration of diabetes	CCT (µm)
<10 years	561.45 ± 36.4
≥10 years	565.78 ± 39.0
P value	0.522

Table 4. CCT of the diabetic patients according to HbA1c levels.

HbA1c level	CCT (µm)
<7%	555.02 ± 32.5
≥7%	570.61 ± 40.3
P value	0.021*

* Statistically significant (independent sample t test)

is important. If diabetes somewhat causes central corneal thickening, does CCT correlate with disease severity? To find the answer, our patients were classified according to retinopathy status. The results demonstrated that retinopathy severity had no effect on CCT. Only patients with mild to moderate nonproliferative retinopathy had significantly higher CCT values than the patients with diabetes but with no retinopathy.

Does glycaemic control have any effect on CCT? Recently HbA1c level has been emphasised as a valuable marker of glycaemic control. Haemoglobin is a protein found in red blood cells. In the bloodstream, glucose sticks to the red pigment in haemoglobin forming A1c (HbA1c). Each red blood cell lives for 8-12 weeks. During this time, the more glucose in blood, the more it will stick to the haemoglobin. HbA1c levels in blood provide guidance as to what the average blood glucose level has been for the past 2-3 months. Therefore, regular HbA1c testing tracks recent glycaemic control. We investigated HbA1c values and their correlation to CCT. Patients with higher HbA1c levels (≥7%) had higher CCT than the patients with lower HbA1c levels (<7%). In contrast to our results, Larsson et al (6) and Keoleian et al. (10) did not delineate any correlation between HbA1c and CCT.

It has been shown that abrupt correction of hyperglycaemia can result in transient hyperopia. Research on phakic and aphakic diabetic individuals indicated that changes in the function and morphology of the lens were responsible for such

Table 5. Previous studies on corneal alterations in diabetic patients.

Study	Cohort	Thickness measurement method	Central Corneal Thickness (CCT)*	Additional corneal findings
Busted et al.[8] (1981)	81 type I diabetics 49 control subjects	Haag-Streit pachometer	Central cornea was thicker [544 µm in nonproliferative, 566 µm in proliferative retinopathy] than control subjects [527 µm]	Folds in the central endothelial layer of diabetic eyes.
Schultz et al.[11] (1984)	31 type I diabetic eyes 46 type II diabetic eyes 75 control eyes	Specular microscope	CCT was similar in both type I [540 µm] and type II [530-540 µm] diabetics when compared to controls [540 µm for the controls of type I diabetics, 530-570 µm for the controls of type II diabetics]	Increased pleomorphism, polymegathism, decreased endothelial cell density in type I diabetics, increased pleomorphism, polymegathism, but no difference in endothelial cell density in type II diabetics.
Keoleian et al.[10] (1992)	14 type I diabetics 14 control subjects	Specular microscope	CCT [560µm] was similar to control subjects [560 µm]	Increased pleomorphism, polymegathism, increased corneal autofluorescence, undisturbed endothelial cell density.
Larsson[6] (1996)	49 type I diabetics 60 type II diabetics 40 control subjects	Specular microscope	CCT was alike in type I [580 µm] and type II [570 µm] diabetics. Central cornea was thicker in type I diabetics than controls [550 µm]. CCT was alike in type II diabetics and controls [560 µm]	Polymegathism, pleomorphism and increased corneal autofluorescence in type I diabetics. No change in type II diabetics.
Roszkowska et al.[9] (1999)	30 type I diabetics 45 type II diabetics 62 control subjects	Specular microscope	CCT was higher in both type I [580 µm] and type II [570 µm] diabetics when compared to controls [540 µm for type I controls] [550 µm for type II controls]	Increased pleomorphism, polymegathism, decreased endothelial cell density in both type I and type II diabetics.
Rosenberg et al.[3] (2000)	23 type I diabetics 9 control subjects	Confocal microscope	Patients with severe retinopathy had significantly higher CCT [596 µm] than control group [527µm]	Thicker cornea in diabetic patients without neuropathy.
Lee et al.[2] (2006)	200 insulin-dependent diabetics 100 control subjects	Ultrasound pachymetry	Diabetics had thicker cornea [588 µm]. Disease duration correlated with CCT	Less corneal cell density, hexagonality, higher coefficient of variation in cell size in diabetes.

refractive changes. One would expect that hyperglycaemia could affect corneal hydration as well and cause qualitative and quantitative corneal changes such as change in refractive index, curvature, and thickness (14,15). Higher HbA1c as a marker of poor glycaemic control was associated with thicker corneas in our study. One would also expect that disease severity and duration would affect corneal thickness likewise. However, it was not possible to detect any effect of these factors on corneal thickness. This might be due to different homeostatic changes taking place during the chronic course of diabetics. Therefore, longitudinal follow-up studies need to be performed in order to ascertain the exact relationship of blood glucose with the cornea.

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