Original Article / Özgün Araştırma

Associations Between Glycosylated Hemoglobin (HbA1c) Level and Central Corneal and Macular Thickness in Diabetic Eyes Without Retinopathy

Retinopatisi Olmayan Diyabetik Gözlerde Glikolize Hemoglobin (HbA1c) Düzeyi ile Merkezi Korneal ve Maküler Kalınlık Arasındaki İlişki

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Abstract

Objective: The comparison of a central corneal (CCT) and central foveal thickness (CMT) of type 2 patients with diabetes with a healthy control group and determine the difference according to fasting blood glucose (FBG), hemoglobin a1c (HbA1c) levels and time of diabetes.

Materials and Methods: Fifty patients with diabetes without retinopathy and 47 healthy controls of similar age and gender were compared. The mean of three consecutive corneal thickness measurements at the central cornea was obtained by the Pentacam HR imaging system (Oculus Optikgeräte GmbH, Wetzlar, Germany) and macular thickness was obtained by Heildenberg optical coherence tomography (OCT). The fiber Bragg grating (FBG) and HbA1c levels of all participants were evaluated. The analysis was performed on the right eye.

Results: Groups were statistically similar in terms of age and gender ($p>0.05$). Patients with diabetes had significantly higher FBG and HbA1c values than controls and the percentage of patients with HbA1c values less than 8% in Type 2 diabetes mellitus was significantly lower than healthy controls ($p<0.001$). Visual acuity logarithm of the minimum resolution angle of patients with diabetes was significantly lower than that of controls ($p=0.034$). However, similar results were obtained in both groups in terms of CCT and CMT values ($p>0.05$).

Conclusion: In our study, diabetic participants without DR had no difference at CCT and CMT between non-diabetic controls. This result shown that the macula and corneal thickness cannot be used as indicators of retinopathy and keratopathy.

Öz

Amaç: Tip 2 diyabetik hastaların santral kornea (SKK) ve maküler foveal kalınlıklarının (SMK) sağlıklı bir kontrol grubu ile karşılaştırılması ve açlık kan şekeri (AKŞ), hemoglobin A1c (HbA1c) düzeyleri ve diyabet süresine göre farkın belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Retinopatisi olmayan 50 diyabetik hasta ve benzer yaş ve cinsiyet özelliği gösteren 47 sağlıklı kontrol karşılaştırıldı. SKK'de art arda üç kornea kalınlığı ölçümünün ortalaması Pentacam HR ımaging system (Oculus Optikgeräte GmbH, Wetzlar, Germany) ile ve maküla kalınlığı Heildenberg optik koherens tomografi (OKT) ile elde edildi. Tüm katılımcıların AKŞ ve HbA1c seviyeleri değerlendirildi. Analiz sağ göze yapıldı.

Bulgular: Yaş ve cinsiyet açısından gruplar istatistiksel olarak benzerlik göstermekteydi (p>0,05). Diyabetik hastaların AKŞ ve HbA1c değerleri sağlıklı kontrollere göre anlamlı olarak yüksek ve HbA1c değerleri %8'in altında olan tip 2 diabetes mellitus hastalarının yüzdesi sağlıklı kontrollerden anlamlı olarak düşüktü (p<0,001). Diyabetik hastaların görme keskinliği (LogMAR), sağlıklı kontrollere göre anlamlı derecede düşüktü (p=0,034). Öte yandan SKK ve SMK değerleri açısından her iki grupta da benzer sonuçlar elde edildi (p>0,05).
Sonuç: Çalışmamızda retinopatisi olmayan diyabetik katılımcılarda, diyabetik olmayan kontroller arasında SKK ve SMK açısından fark yoktu. Bu sonuç maküla ve kornea kalınlığının retinopati ve keratopatinin bir göstergesi olarak kullanılamayacağını göstermiştir.

Introduction

Diabetes mellitus (DM) is a multisystemic disease as a result of microvascular and macrovascular pathologies. Ocular complications of DM are anterior ischemic neuropathy, glaucoma, cataract, retinal vessel occlusions, and retinopathy (1,2). Although retinal involvement is very common in DM, it is expected that the cornea will be affected (3,4). It can be seen in corneal pathologies such as corneal epithelial defects, recurrent epithelial erosion, basement membrane disorders such as keratitis or ulcer development, epithelial disorders, endothelial cell number and morphology disorders, and decreased corneal sensitivity (5).

Glycosylated hemoglobin (HbA1c) level is a marker of glycemic control and it a critical indicator of the management of DM (6). Optical coherence tomography (OCT) is extensively used to measure retinal thickness and the Pentacam HR is an anterior segment tomography and it is used to evaluate non-contact corneal thickness (7).

In this study, we aimed to evaluate the central cornea and macular thickness in diabetic eyes without retinopathy and keratopathy according to the effect of HbA1c level of DM duration.

Materials and Methods

This study which was a cross sectional, prospective study, conducted in the University of Health Sciences Turkey, Ulucanlar Eye Training and Research Hospital between December 2019 and June 2020. The study was approved by the Institutional Ethics Committee (Ankara Training and Research Hospital, no: E-19-42, date: 26.12.2019) and in accordance with the principles of the Declaration of Helsinki. A signed informed consent form was obtained from all volunteers. There were 50 participants with type 2 DM patients without retinopathy and 47 non-diabetic age-sex matched control subjects. We divided the diabetic patients into two groups according to the HbA1c levels (≥8% or <8%) and disease duration.

The mean of three consecutive central corneal thickness (CCT) measurements was obtained by the Pentacam HR Imaging System and central macular thickness (CMT) was obtained by Heildenberg OCT in all participants.

Patients who were followed up in the retina department of in the hospital, met the study criteria and accepted to participate in the study were invited to the study. Patients with DM type 2 without retinopathy were older than 18 years and younger than 80 years of age, without previous eye surgery, no history of glaucoma, intraocular inflammation or infection and chronic topical drug use. The history of intraocular surgery, focal or pan-retinal photocoagulation and periocular or intravitreal injection use of contact lens, regular eye drop usage, spherical and cylindrical refractive errors >±3.00 D were excluded. Macular disease such as clinically significant macular edema, proliferative diabetic retinopathy and any retinal or retinal vascular disease were not included in the study. We included only the right eyes in our study.

Best-corrected visual acuity (BCVA), intraocular pressure measurement, detailed biomicroscopic and fundus examination with +90 D condensing lens were undergone in all subjects. The BCVA measurements were made on a Snellen chart and the data was transformed to logarithm of the minimum resolution angle (LogMAR). Venous blood samples were taken to determine the level of HbA1c. Fasting blood glucose (FBG) was measured simultaneously with HbA1c. Macular thickness measurements were performed using the Heildenberg OCT by trained the same technician after pupil dilatation with tropicamide 1% and cyclopentolate HCL 1%. The Pentacam Scheimpflug imaging system (Pentacam HR, Oculus, Wetzlar, Germany) provides two-dimensional images

that obtain the three-dimensional structure of the cornea by software analysis with using rotating cameras for detailed analysis through the optic axis from the epithelial surface of the cornea to the posterior capsule of the lens. In this system, CCT is obtained from the measurement difference in the anterior and posterior elevation maps (8).

Statistical Analysis

We evaluated research data on the computer via "SPSS for Windows 22.0 (SPSS Inc, Chicago, IL)". Visual (histogram and probability plots) and analytical tests such as Kolmogorov-Smirnov/Shapiro-Wilk were used for analysis for normal distribution variables, while student's t-test was used for analysis of non-normal distributions. Pearson's chi-square test and Fisher's Exact test was used for categorical variables. The Mann-Whitney U test was preferred for the analysis of two dependent groups. In order for the p value to be significant, it had to be below 0.05.

Results

A total of 97 individuals, 50 of whom were diagnosed as Diabetus mellitus type-2 and 47 healthy control subjects were examined. In Table 1, where the descriptive characteristics of the study groups are given, a similar distribution was observed in terms of age and gender (p>0.05) and HbA1c and FBC parameters were statistically higher in type 2 DM group (p<0.001 for both). Visual acuity values of diabetic group were (mean ± standard deviation) 0.93±0.18 (minimum-maximum: 0.2-1.0) and 0.98±0.09 (0.5-1.0) in control group and statictically significantly lower in the diabetic group (p=0.034). We classified the diabetic group according to HbA1c levels and duration of diabetes (Table 2, 3). There was no statistically significant difference between the groups with HbA1c levels ≥8% or <8% group in terms of age, gender, HbA1c and FBG levels (Table 2). At the same time, between subgroups of HbA1c levels, no difference was found in terms of CCT, CMT, and BCVA (Table 2). When we classified the diabetes group according to the duration of DM, 16 (34%) of 47 patients were diagnosed with DM over 10 years. The average duration of DM was 9,8 years (2-25 years) in HbA1c ≥8% group and 9,6 years (1-25 years) in HbA1c levels >%8 group. There was no difference in age, gender, fasting blood sugar and HbA1c levels between groups with diabetes duration (Table 3).

CCT values were 544.7±24.5 (507-623) µm in diabetic group and 543.2±34.6 (444-600) µm in control group. CMT values were 275.1±45.9 (214-443) µm in diabetic group and 269.6±24.8 (232-352) µm in control group. CCT and CMT values were not statistically significant different between the groups (p>0.05). In addition, it was observed that DM duration and level of HbA1c were not effective on BCVA, CCT and BMT values (p>0.05) (Table 4, 5).

Discussion

Multiple organ failure in diabetic patients were as a result of microvascular and macrovascular pathologies which are caused by hyperglycemia.

Table 1. Distribution of some descriptive characteristics between the study groups

	Type 2 DM (n=50)	Control (n=47)	p
Age (year), mean ± SD (min-max)	57.5±9.2 (35-75)	54.3±9.6 (34-76)	0.099a
Gender, n (%)			
Female	14 (28.0)	21 (44.7)	0.087b
Male	36 (72.0)	26 (55.3)	
FBG (g/dL), mean ± SD (min-max)	173.3±74.2 (80-372)	101.8±15.0 (76-148)	<0.001c**
HbA1c (%), mean ± SD (min-max)	8.1±2.0 (5.7-13.3)	5.8±0.4 (5.0-6.5)	<0.001c**
HbA1c group, n (%)			
<6%	4 (8.0)	33 (70.2)	
6-8%	30 (60.0)	14 (29.8)	<0.001b**
>8%	16 (32.0)	0	

n: Number of individuals, %: Percentage, SD: Standard deviation, FBG: Fasting blood glucose, DM: Diabetes mellitus, Min-max: Minimum-maximum, [a]Student's t-test, [b]Pearson chi-square test, [c]Mann-Whitney U test, *p<0.05, **p<0.01

Table 2. Distribution of age, sex and FBG between HbA1c groups of patients with type-2 DM

	Total (n=50)	HbA1c		p-value
		<8% (n=33)	≥8% (n=17)	
Age (year), mean ± SD (min-max)	57.5±9.2 (35-75)	57.4±8.9 (35-75)	57.7±10.2 (37-75)	0.920[a]
Gender, n (%)				
Female	14 (28.0)	8 (24.2)	6 (35.3)	0.511[b]
Male	36 (72.0)	25 (75.8)	11 (64.7)	
DM duration (year), mean ± SD (min-max)	9.7±5.9 (1-25)	9.8±6.2 (2-25)	9.6±5.6 (1-25)	0.918[c]
DM duration group, n (%)				
<10 year	34 (68.0)	23 (69.7)	11 (64.7)	0.720[d]
≥10 year	16 (32.0)	10 (30.3)	6 (35.3)	
FBG (g/dL), mean ± SD (min-max)	173.3±74.2 (80-372)	147.5±49.8 (83-340)	223.4±88.8 (80-372)	0.006[c]**

n: Number of individuals, %: Percentage, SD: Standard deviation, FBG: Fasting blood glucose, DM: Diabetes mellitus, Min-max: Minimum-maximum, [a]s: Student's t-test, [b]Fisher's Exact test, [c]Mann-Whitney U test, [d]Pearson chi-square test, *p<0.05; **p<0.01

Table 3. Distribution of age, sex and fasting blood sugar between DM duration groups of patients with type 2 DM

	Total (n=97)	DM duration		p-value
		<10 year (n=34)	≥10 year (n=16)	
Age (year) mean ± SD (min-max)	57.5±9.2 (35-75)	56.6±9.2 (35-70)	59.4±9.2 (42-75)	0.320[a]
Gender n (%)				
Female	14 (28.0)	12 (35.3)	2 (12.5)	0.175[b]
Male	36 (72.0)	22 (64.7)	14 (87.5)	
HbA1c (%) mean ± SD (min-max)	8.1±2.0 (5.7-13.3)	7.9±1.9 (5.7-12.1)	8.6±2.2 (6.5-13.3)	0.248[c]
FBG (g/dL) mean ± SD (min-max)	173.3±74.2 (80-372)	163.4±73.2 (80-372)	194.2±74.3 (110-340)	0.094[c]

n: Number of individuals, %: Percentage, SD: Standard deviation, FBG: Fasting blood glucose, min-max: Minimum-maximum, DM: Diabetes mellitus, [a]Student's t-testi, [b]Fisher's Exact test, [c]Mann-Whitney U test

Table 4. Distribution of visual acuity, central corneal and macular thickness between HbA1c groups of patients with type 2 DM

	Total (n=50)	HbA1c		p-value
		<8% (n=33)	≥8% (n=17)	
	Mean ± SD (min-max)	Mean ± SD (min-max)	Mean ± SD (min-max)	
BCVA (LogMAR)	0.93±0.18 (0.2-1.0)	0.94±0.16 (0.3-1.0)	0.90±0.22 (0.2-1.0)	0.724[a]
CCT (µm)	544.7±24.5 (507-623)	543.9±25.6 (507-623)	546.2±22.7 (507-588)	0.757[b]
CMT (µm)	275.1±45.9 (214-443)	275.8±51.2 (214-443)	273.7±34.8 (235-391)	0.674[a]

n: Number of individuals, SD: Standard deviation, BCVA: Best-corrected visual acuity, CCT: Central corneal thickness, CMT: Central macular thickness, min-max: Minimum-maximum, LogMAR: Logarithm of the minimum resolution angle, [a]Mann-Whitney U test, [b]Student's t-test

Ocular complications of DM are the primary reason for progressive blindness in the world (9,10). Recently, 4,2 million humans were affected by diabetes which is a vital and progressive reason for blindness (11). Cornea and retina are the most affected ocular tissues by diabetes regulation and diabetes duration. Hence, in this study, we planned to evaluate cornea and macula in eyes without diabetic retinopathy.

Calvo-Maroto et al. (12) found no significant difference in CCT between the diabetic group, which was classified according to the period of diabetes, regardless of the presence of retinopathy and

Table 5. Distribution of visual acuity, central corneal and macular thickness between HbA1c groups of patients with type 2 DM

	Total (n=97)	DM duration		p-value
		<10 year (n=34)	≥10 year (n=16)	
	Mean ± SD (min-max)	Mean ± SD (min-max)	Mean ± SD (min-max)	
BCVA (LogMAR)	0.93±0.18 (0.2-1.0)	0.95±0.12 (0.5-1.0)	0.88±0.26 (0.2-1.0)	0.269[a]
CCT (μm)	544.7±24.5 (507-623)	545.5±25.7 (507-623)	543.0±22.2 (507-585)	0.737[b]
CMT (μm)	275.1±45.9 (214-443)	270.2±40.1 (224-442)	285.6±56.4 (214-443)	0.204[a]

n: Number of individuals, SD: Standard deviation, BCVA: Best-corrected visual acuity, CCT: Central corneal thickness, CMT: Central macular thickness, min-max: Minimum-maximum, LogMAR: Logarithm of the minimum resolution angle, [a]Mann-Whitney U Test; [b]Student's t-test

the healthy control group. Similarly, we could not find difference between study groups in terms of CCT. Choo et al. (13) revealed that HbA1c level and severity of retinopathy had no effected to CCT, but they found endothelial differences. Besides, the same study reported that the HbA1c level did not affect endothelial morphology. Inoue et al. (14) similarly, they did not detect any difference in corneal thickness even at different stages.

However, Gao et al. (15) found that diabetes duration (<5, 5-10,>10 years) had a significant increase on CCT in 360 eyes of 180 patients. We thought that the most important reason for the difference between the study groups in this study is the high number of patients with more than a decade of diabetes duration (50% of patients). As the duration of diabetes increases, the rate of retinopathy increases. Since we especially preferred patients without retinopathy, the number of patients with diabetes duration more than 10 years was less in the study.

In a study of Toygar et al. (16), diabetic patients were classified based on the existence and severity of retinopathy. They reported that CCT of all diabetic was higher than a control group, but these results did not show any correlation with the presence of retinopathy. Similar to our data, there was no difference in CCT between study groups.

Lee et al. (17) noticed that in diabetic group with normal fundus or background diabetic retinopathy had higher CCT values compared to the control group and also was found that the disease duration >10 years was significantly higher from those less than 10 years. They emphasized that the duration of diabetes is effective on the corneal thickness.

In our study, there was no difference in CCT in both study group and HbA1c levels-disease duration subgroups. It can be interpreted that there will be no significant change in the corneal thickness in eyes without retinopathy. Furthermore, HbA1c levels and disease duration did not affect changes of cornea thickness in these eyes. It is not clear which mechanism about CCT is more prominet in eyes without retinopathy.

In Srinivsan's study, 60% of patients with non-proliferative diabetic retinopathy (NPDR) with only microaneurysms and the others who had mild NPDR were crosschecked with healthy group. They could not detect any difference between the groups in terms of CCT and CMT, supporting our data (18). Yeung et al. (6) found no statistically significant difference regarding the macular thickness between the diabetic patient group without retinopathy and the diabetic patient group with retinopathy without macular edema.

Dai included a large number of patients, no difference was found between groups with early DR and without retinopathy related to macular thickness (19). However, the macula was found to be significantly thicker in patients with moderate or worse retinopathy. This situation supports the result we achieved in our working group. We included diabetic patients without retinopathy to study whether macular thickness would be a marker without retinopathy in the macula, and we attributed the absence of a significant difference.

De Clerck et al. (20) who compared pre-diabetics groups, diabetes without retinopathy with a control group, found that macula thickness of pre-diabetic patients decreases prominently, besides, it is higher when diabetes becomes obvious clinically, they attributed this to neurodegenerative changes.

In a study conducted in Singapore which the patients with diabetic retinopathy at different stages, macular thicknesses in patients with no or mild diabetic retinopathy were not found different from

the control group. This situation shows the effect of retinopathy stage on macular thickness and is similar to our results. They also found no significant difference in macular thickness between moderate and severe DR patients without macular edema. In this study, no relation was found between macular thickness and HbA1c level. We included patients without retinopathy to determine whether macular thickness was a marker in the early period, and similarly, we revealed that the macula had no early effect (21).

Yolcu et al. (22) when the central macular thickness of type 1 DM patients with a diabetes duration of 6.1±2.8 years and without retinopathy and the control group were compared, was found no differences. This study, which is similar to us in terms of the duration of diabetes and retinopathy of its participants, supports our results.

There are many studies on the effects of diabetes on corneal thickness and macular thickness. As mentioned above, different results have been reported in these studies. We think that this difference is due to the variability of the retinopathy stages in diabetic patients. In addition, it should be considered that DM may have a complex effect on tissues. With the developing technology over time, the macula can be evaluated in more detail and a clearer result can be obtained.

When we examine the studies in the literature and evaluate our data, we think that the most important factors in corneal and macular thickness in diabetic retinopathy are the advanced stage of retinopathy and the duration of diabetes >10 years. The fact that our diabetes group is less than 10 years old and that we include advanced retinopathy groups are the most important limiting factors of our study. As a result of the study, although there was no significant difference between the diabetic group without retinopathy and maculopathy and the control group in terms of CCT and CMT, the significant difference in visual acuity makes us think that there are some changes in terms of microstructure. In a study, the visual acuity of the diabetic group without clinical retinopathy was found to be lower than that of the control group, and a difference was found in the level of capillary plexus flow between the groups examined by OCT angiography, even though there was no difference between the foveal avascular zones (23).

To the best of our knowledge, we did not find any study evaluating the effect of both macular and corneal thickness. We compared that type 2 DM patients with no retinopathy and healthy control group considering the duration of HbA1c and diabetes. In the results of study, no effect was found between macular and corneal thicknesses of HbA1c level and diabetes duration.

Conclusion

In light of the findings of this study, it can be assumed that DM may not cause changes in the thickness of macula and cornea in eyes without retinopathy. In conclusion, DM has different effects on each ocular tissue as macular and corneal thickness. It should not be used as an indicator of retinal and corneal involvement. Studies with more detailed examinations of the microstructure will be more illuminating.

Ethics

Ethics Committee Approval: The study was approved by the Ankara Training and Research Hospital Clinical Research Ethics Committee (no: E-19-42, date: 26.12.2019).

Informed Consent: The written consent of the participants was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.K., D.Ö.S., Ç.İ., Y.Ö.E., Concept: B.K., D.Ö.S., Y.Ö.E., Design: B.K., Y.Ö.E., Data Collection or Processing: B.K., D.Ö.S., Ç.İ., Analysis or Interpretation: B.K., D.Ö.S., Ç.İ., Literature Search: B.K., D.Ö.S., Ç.İ., Y.Ö.E., Writing: B.K., Y.Ö.E.

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